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THE BONE MARROW IN ANÆMIA.[*]

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THE response in pernicious anæmia to the administration of potent liver extracts has now become commonplace, and in the absence of an infection, impaired renal function or thyreoid insufficiency, this response can be predicted with unfailing regularity. Such a response by the sufferers from this disease, many of whom when first seen are *in extremis*, is no wit less dramatic than the triumphs of surgery. However, as a result of dramatic surgery, more often than not, the surgeon acquires a magnificent and permanent trophy (such as Gordon-Taylor's[1] innominate bone with a twenty-pound chondroma attached), while in hæmatology the trophies are usually microscopic, and most are, alas, not permanent.

If a book were written on "The Dramatic in Medicine", prominence would naturally be given to the effect of liver therapy in pernicious anæmia; this includes the alteration in the general condition of the patient, the alterations in the peripheral blood and the alterations in the bone marrow; but, being most obvious, the alteration in the general condition would probably receive most attention. While there are few medical diseases in which such a change may be wrought in the general condition of the patient within a fortnight, yet the disappearance of the dyspnœa, the weakness, the slight icterus and the deadly pallor (literally deadly if liver therapy is not soon commenced) are no more striking than the changes produced in the blood and in the bone marrow.

The peripheral blood in pernicious anæmia presents the reticulocytogenic response to liver with the subsequent increase in the number of erythrocytes and in the hæmoglobin value, and with the restoration to normal of the mean corpuscular volume and hæmoglobin content, the number of platelets and neutrophile cells and the lobulation of the neutrophile cells. These changes in the peripheral blood, which may be followed at frequent intervals and with practically no inconvenience to the patient, commence before there is any demonstrable change in the general condition, and accordingly have been used as an early guide to the potency of the liver preparation and of the patient's ability to respond to it. Although the reticulocyte response does not reach a maximum until the fourth to seventh day, depending on the severity of the anæmia and on the amount of liver administered, it is sometimes advantageous to be able to determine more rapidly the efficacy of the liver preparation and the patient's response to it. This may be accomplished by sternal marrow examinations within twenty-four hours of the commencement of liver therapy. The bone marrow of an untreated patient with pernicious anæmia is hyperplastic, usually extends throughout the long bones and contains a high percentage of promegaloblasts and megaloblasts, and many of the cells of the granular series are of the "giant stab" form. That this bizarre picture should rapidly be restored to normal by the injection of a few millilitres of liver extract is astonishing; but the factors responsible for this change still remain obscure.

The bone marrow in the secondary hypochromic anæmias is entirely different from that of pernicious anæmia, for while there is a great increase in the number of primitive red cells, these cells are still normal in type—that is, of the definitive series—and there is no alteration in the cells of the granular series.

[*] This work was carried out during the tenure of a senior Fellowship in Surgery, Prince Henry Hospital, Sydney.

Strangely enough, although the possibility of repeated marrow examinations has been stressed as one of the chief advantages of sternal puncture compared with trephining of the sternum, yet the literature contains few reports of serial marrow examinations. Several cases of pernicious anæmia have been reported in which the marrow has been examined before and on a few occasions after the commencement of liver therapy; but Bock and Malamos's[2] case appears to be unique, in that the marrow was examined before the commencement of liver therapy, sixteen times in the following month and then three times in the next three months.

In this paper the literature dealing with the bone marrow in pernicious anæmia and in other megalocytic anæmias is reviewed, and serial bone marrow findings in three cases of pernicious anæmia, in one case of megalocytic anæmia associated with a carcinoma of the œsophagus, and in one case of anæmia due to chronic blood loss are described. The marrow in a probable case of subacute combined degeneration of the spinal cord unassociated with macrocytic anæmia is also described.

Nomenclature of the Marrow Cells in the Anæmias.

Since the development of the marrow cells from immature to mature forms is accompanied by but slight changes from one generation of cells to the next, the nomenclature of these cells must necessarily tend to be somewhat confused, depending as it does on an attempt to divide the process of development of the marrow cells into definite stages, which in reality do not exist. Nevertheless, there has emerged a generally acceptable terminology for the more mature cells of the marrow; but concerning the classification of the more primitive cells, both in the adult and in the embryo, and of pathological cells, there is as yet no unanimity of opinion. Of all the cells referred to in hæmatology, none have such a wide variety of terms applied to it as the large cells (up to 15μ) which contain deeply basophilic, non-granular cytoplasm, large nuclei with fine chromatin network and one or more nucleoli. These are said to be the undifferentiated stem cells; but along with this lack of agreement in the terminology of these cells there is also considerable divergence of opinion between the various schools of hæmatologists as to their exact function.

Maximow[3] identified these primitive stem cells as large lymphocytes (or hæmocytoblasts) from which all the other blood cells were derived. Pappenheim classed these cells as lymphoidocytes (the chief difference from Maximow's lymphocyte was the increased basophilia of the cytoplasm). Pappenheim's lymphoidocyte was also thought to give rise to both the red and the white cells. Ferrata described a cell corresponding to Pappenheim's lymphoidocyte, which he called a hæmohistioblast, and which he considered gave rise to all types of blood cells. In addition Ferrata described another cell, which was supposed to be intermediate between the mesenchymal cells and the hæmohistioblast, and which he considered gave rise to the primitive erythroblasts in the early embryo and to the hæmohistioblast in the later embryo.

In opposition to these monophyletic schools there are the polyphyletic schools; their members include Naegeli,[4] who believed that the truly indifferent stem cells were to be found only in the embryonic mesenchyme and that even the first generation of cells derived from the mesenchyme were irreversibly directed towards the adult type. In erythropoiesis Naegeli also believed that two cells were produced from the mesenchyme: (i) the promegaloblast, which developed into the megaloblast and the adult megalocyte, and (ii) the pronormoblast, which developed into the normoblast and the adult erythrocyte. Naegeli introduced the term myeloblast as the specific parent cell of the granular series (including the megakaryocyte and the monocyte). He considered that the lymphocytic series was derived directly from the mesenchymal cells. Doan, Cunningham and Sabin[5][6][8] favoured the theory of an independent origin of the red and white blood cells from the endothelial and reticular cells respectively, without the intermediation of a common stem cell. Their conception was of a direct origin of the megaloblast from the endothelial cells, while the primitive cell which developed from the reticular cells was thought to give rise to the myeloblasts, monoblasts and lymphoblasts, which were type specific.

In 1880 Ehrlich introduced the terms "megaloblast" and "gigantoblast" for the very large nucleated red cells of the early embryo and for similar cells occasionally found in the blood in pernicious anæmia. These cells were described (Ehrlich and Lazarus[7]) as being from two to four times the size of normal red blood corpuscles, with the hæmoglobin extending throughout the greater part of the cell and frequently showing some degree of "anæmic degeneration", and with the nucleus rounded, ill-defined and larger than that of the normoblast, but not occupying so large a portion of the cell as the latter. The nuclei of the megaloblasts were said to differ from those of the normoblasts by their finely differentiated structure and by their small capability of taking up nuclear stains.

The primitive stem cells have been given a variety of names by different hæmatologists; but the term "megaloblast" has been applied to several different cells, and it is partly because of this that the problem of the origin of the megaloblast and its relation to the other blood and marrow cells is so complex and confusing. The discovery by Minot and Murphy of the therapeutic effectiveness of liver in pernicious anæmia has not solved the problem of the megaloblast, although it has helped to clarify it.

Doan, Cunningham and Sabin[5][6][8] applied the term "megaloblast" to the first few generations of cells in the red cell series derived from the fixed endothelial cells in both embryonic and adult life. They described these cells in the chick and the rabbit embryo as having a basophilic cytoplasm and a large nucleus poor in chromatin and containing a conspicuous nucleolus. With nuclear and cytoplasmic changes towards maturity these authors recognized the stages of the erythroblast and of the normoblast. Peabody[9] has followed Doan, Cunningham and Sabin in their conception of the megaloblast.

Maximow[3] was apparently the first to question the unity of the primitive hæmoglobinized red cells of the early embryo and the large hæmoglobinized cells of pernicious anæmia—that is, whether the two cells grouped together by Ehrlich as megaloblasts bore only a superficial resemblance to each other or were identical. Turnbull[10] also doubted whether the abnormal shift to the left of ripening of the cytoplasm after birth (in pernicious anæmia) represented a true return to the normal conditions and processes of erythropoiesis in the early embryo. Recently the subject of normal hæmopoiesis in the embryo has been investigated by Gilmour,[11] who uses the term "hæmocytoblast" for the most primitive cells whose potentiality of differentiation is directed to hæmopoiesis only. Gilmour[11] uses the term "megaloblast" for large primitive red cells, in which hæmoglobin is visible, and which will, he states, form as a rule megalocytes, but sometimes normocytes. Thus Gilmour did not recognize promegaloblasts and basophilic megaloblasts, but divided the megaloblasts into early, intermediate and late according to the preservation of the nuclear structure. Gilmour[11] discussed only normal fœtal and neonatal hæmopoiesis; but even so, the presence of hæmoglobin in the cytoplasm may be insufficient grounds for the classification of cells as megaloblasts. The importance of nuclear rather than cytoplasmic morphology for differentiating between cell types is discussed by Nordenson,[12] who has shown that pronormoblasts and normoblasts (of the definitive series) may prematurely develop hæmoglobin in the anæmias. The recognition of megaloblasts in sections is also complicated by the fact that Jones[13] has demonstrated that the cytoplasm of the megaloblasts in pernicious anæmia may occasionally contain azurophilic granules. Again, Israels,[14] working with air-dried smears of fresh marrow, has described three patients suffering from hæmolytic anæmia, one suffering from hæmolytic jaundice and one suffering from pernicious anæmia in therapeutic remission; the bone marrow of all these patients contained "intermediate normoblasts" (of the definitive series) containing varying amounts of

hæmoglobin in the cytoplasm. Histiological sections were used by Gilmour,[11] and therefore in his preparations the fine nuclear differences of the developing red cells, demonstrable in smears or imprints, would not have been present. Gilmour[11] described two types of megaloblasts—the primitive and the definitive—respectively occurring before and after the ten-millimetre stage of the embryo, but differing from each other in the morphology of the nucleus. It would appear that his primitive megaloblast corresponds to Ehrlich's megaloblast of the embryo and that his definitive megaloblast belongs to the definitive normoblastic series. Although his primitive megaloblasts resemble somewhat the orthochromatic megaloblasts of pernicious anæmia in relapse, there is no evidence to suggest that they are identical. In the embryo, Turnbull[10] has limited the term "megaloblast" to primitive red cells found before the ten-millimetre stage.

The term "proerythroblast", introduced by Ferrata and Rinaldi[15] and by Schulten,[16] was applied by Israels[17] to the earliest cell that definitely belongs to the red cell series. Israels[17] and Dameshek and Valentine[18] defined this cell as "large (13 to 22 microns, average 18 microns) with a nucleus occupying most of the cell body and having dark blue cytoplasm. The nucleus has a scroll-like, rather pale staining, fine chromatin resembling a mass of unravelled yarn." Israels[17] suggested that the hæmocytoblast gave rise to the proerythroblasts and to the cells of the white cell series. His developmental scheme showed the first generation of red cells derived from the hæmocytoblasts as the proerythroblasts, from which either normoblastic or megaloblastic development may proceed. (Dameshek and Valentine[18] used the term "erythrogone" as synonymous with Israels's proerythroblast.) Jones,[19] on the other hand, derived both the megaloblastic and the normoblastic series from the myeloblast and from the undifferentiated reticulum cells. Israels's proerythroblast of pernicious anæmia bone marrow appears to resemble the promegaloblast (or premegaloblast) of other authors.[13][15][20] The characteristics of the promegaloblasts were summarized by Nordenson[12] as large cells, with abundant deeply basophilic non-granular cytoplasm in which commencing hæmoglobin formation might sometimes be observed, with a very loose, finely meshed chromatin net; sharply defined nucleoli were always present. The term "megaloblast" was applied by Israels[17] to a series of cells, found in the marrow only when the proper activity of the "liver principle" was in abeyance, which passed in gradual stages from an immature non-hæmoglobinized to a mature hæmoglobinized form, being without nucleoli and having at first an open network arrangement of the chromatin, but later becoming pyknotic. Nordenson[12] used the term "megaloblast" to refer to the same series of cells as Israels;[17] but he differed from Israels in that he differentiated between the pronormoblasts (progenitors of the definitive normoblasts) and the promegaloblasts of pernicious anæmia. Nordenson[12] described the pronormoblasts as relatively large cells with deeply basophilic cytoplasm without granulation and usually without hæmoglobin. The nucleus is rather large with a quite loose and coarsely meshed chromatin network, rich in oxychromatin and often containing rather sharply defined nucleoli. The differentiation of pronormoblasts from promegaloblasts, which depends on their nuclear structure, may, according to Nordenson,[12] sometimes present difficulties. The figures of Israels[17] and of Dameshek and Valentine[18] illustrate the difference in nuclear structure between typical pronormoblasts and promegaloblasts (see Figures I and VIII).

A popular view of the megaloblast is that of Whitby and Britton,[21] who described the megaloblast as a large cell (10μ to 12μ) with non-granular, deeply basophilic cytoplasm and with a large, pale nucleus, containing nucleoli and delicate threads of chromatin, and occupying more than half of the cell. According to Whitby and Britton[21] the cell contains no hæmoglobin, divides to form early erythroblasts (of the definitive series) and is to be found in normal bone marrow. These authors followed Ehrlich's theory that the hæmoglobinized megaloblasts were a reversion to an embryonic cell type. They were also in agreement with the theory that the megaloblasts arose as the result of a maturation factor deficiency—that is, that hæmopoiesis is shifted back to a more primitive but nevertheless normal level. The theory of maturation defects in anæmia has been discussed by Witts.[22] Because of its simplicity, especially for teaching purposes, this theory has enjoyed widespread popularity; but it presupposes that the megaloblast of pernicious anæmia belongs to the definitive series of cells and that it requires the "liver factor" for its further maturation. This theory also does not account for the changes in the cells of the granular series, which do not represent a reversion to an immature type. Among those authors essentially in agreement with Whitby and Britton are Vogel and Bassen,[23] Isaacs,[24] Hynes,[25] Custer,[26] Osgood and Young,[27] McLean,[28] Vogel, Erf and Rosenthal,[29] and Sturgis and Isaacs.[30] Many hæmatologists, including Agress and Downey,[31] Schulten,[32] Nordenson,[12] Jones,[19][33] Turnbull,[10] Scott,[20] Kato[34] and Israels,[14][17] with whom I agree, are not in accord with these authors and consider that the megaloblast is a pathological cell found only in the anæmias due to deficiency of the "liver factor".

The term "erythroblast" has been applied by Gilmour,[11] Israels,[17] Scott,[20] Dameshek and Valentine,[18] and others, to any nucleated cells which may differentiate to form erythrocytes. Nordenson,[12] on the other hand, used the term "erythroblast" for nucleated red blood cells of an indefinite character, rich in hæmoglobin—cells which he had been otherwise unable to identify. Maximow[35] referred to all the young forms of the red blood corpuscles as erythroblasts and classified them by their cytoplasm as basophilic, polychromatic and orthochromatic (or normoblasts). Turnbull[10] applied the term "primary erythroblast" to cells preceding the "basophilic normoblast".

"Erythrogone" and "hæmatogone" are other terms about which there has been much discussion, and as Vogel and Bassen[23] pointed out, they remain the mystery cells of the bone marrow. Although they stated that hæmatogones were increased in untreated pernicious anæmia and in "aregenerative anæmias", Erf and Fine[36] were of the opinion that these cells were probably of the lymphatic series. Kato[34] also classes them with lymphocytes. Dameshek and Valentine[18] and Jaffé[37] used the term "erythrogone" as synonymous with the proerythroblast of Israels.[17] The term erythrogone was introduced by Helly[38] for the primitive stem cell; but as this term is now used with several meanings it would be better discarded. Many of the cells often classed as erythrogones are either micromyeloblasts or primitive lymphocytes.

The term "pronormoblast" has been applied to the most primitive cells of the red cell series seen in the bone marrow of normal subjects and in pathological conditions other than those due to interference with the metabolism of the "liver factor". The pronormoblast is apparently identical with the macroblast of Naegeli,[9] with the macronormoblast of Piney,[39] with the normoblast A of Dameshek and Valentine,[18] with the erythrogone of Helly,[38] and with the proerythroblast of Ferrata and Rinaldi.[15] It is the pronormoblast which has been confused with the megaloblast of pernicious anæmia, and which has been responsible for the statement that the megaloblasts occur in most hyperplastic bone marrows. On the contrary, while there is increasing evidence to disprove this statement, there is no doubt that the pronormoblast may be found in small numbers in the marrow of pernicious anæmia and related conditions.

The characteristic cells of the granular series found in the marrow of pernicious anæmia are the "*grössere pathologische stabkernige Neutrocyten*" of Tempka and Braun,[40] the so-called "giant stab forms". These cells and the macropolycytes of Cooke in the marrow from cases of pernicious anæmia and acute infections have been previously discussed (Wilson[41]).

To recapitulate, the confusion in the nomenclature of the primitive cells of the bone marrow is due, firstly, to the variety of terms applied to the primitive stem cells, secondly, to the use of the term "megaloblast" for several

different cells, and thirdly, to the failure of some authors to distinguish between the megaloblast of pernicious anæmia and the pronormoblasts of hyperplastic marrow of conditions unrelated to pernicious anæmia. The extreme divergence of opinions between hæmatologists is also partly explained by the lack of uniformity of the preparations used. Sections alone do not reveal the finer points of morphology; yet many conclusions have in the past been drawn from such material. Especially does this apply to the embryo. Often there is some difficulty in obtaining fresh embryos under 10 millimetres in length, and when such specimens have been obtained, since it is more difficult to prepare smears or imprints from their tiny organs than to prepare sections, the last-mentioned preparations have in the past been the most popular.

Historical Review.

The bone marrow in pernicious anæmia was first described by Pepper[41] in 1875, and by Cohnheim[42] in 1876. It is interesting to note that because of the general debility in "progressive pernicious anæmia", Pepper suggested the use of cod liver oil. In the past 67 years our knowledge of the bone marrow in this disease has been considerably extended by the work of Ehrlich, Zadek, Peabody, Nordenson, Jones and many others. As the introduction of liver therapy preceded Arinkin's description of sternal puncture, no extensive series of marrow findings from untreated patients suffering from pernicious anæmia exists. More often than not, patients are referred to hospital after one or more preliminary liver injections, and opportunities for obtaining bone marrow from untreated patients suffering from pernicious anæmia have become infrequent.

The morphology of the bone marrow in pernicious anæmia has been repeatedly described and is now clearly defined, except for a few minor details. The hæmoglobinized megaloblasts and their precursors are most obvious in the bone marrow during a relapse. It will be shown, however, that they are not pathognomonic of pernicious anæmia, but have been found in the marrow in some, but not all, of the other macrocytic anæmias.

Before the introduction of liver therapy widespread phagocytosis of the erythrocytes in the bone marrow had been observed by Peabody and Broun[43] and by Doan[44] at autopsy on subjects who had died of pernicious anæmia; but subsequently, Peabody,[9] by the use of tibial puncture, showed that this phagocytosis was an agonal phenomenon.

The effect of liver therapy on the marrow in pernicious anæmia was originally studied by Peabody,[9] who was able to demonstrate in his sections the difference between the megaloblastic bone marrow during a relapse and the normoblastic marrow during a therapeutically induced remission. Previously, Zadek[45] had shown that in spontaneous remissions the marrow became normoblastic in type; this was confirmed by Peabody[9] and Scott.[30] Since then the change from megaloblastic to normoblastic marrow, which occurs in pernicious anæmia within a few days of the commencement of liver treatment, has been described by Segerdahl,[46] by Nordenson,[12] by Bock and Malomos,[3] by Dameshek and Valentine,[13] by Israels,[17] by Weiner and Kaznelson,[47] by Merwe,[48] by Scott,[30] by Schartum-Hansen,[49] by Dameshek,[50] by Vogel and Bassen,[29] and by Isaacs.[51][31] Nordenson's graphs[12] based on differential counts of the blood and bone marrow in cases of pernicious anæmia during therapeutically induced remissions clearly show the changes produced by the liver therapy. This author reported five cases of pernicious anæmia, in which the marrow was examined before treatment and on two, four, five, eight and nine occasions thereafter. These graphs show that the normoblasts, which had been difficult to find in the marrow, rapidly proliferate and dominate the marrow picture, while the megaloblasts and promegaloblasts decrease and then disappear.

Qualitative changes in the cells of the granular series of the marrow in pernicious anæmia, which Fallon[52] regards as diagnostic, were first described by Tempka and Braun[39] and later by Jones,[32][33] by Scott,[30] by Dameshek and Valentine,[13] and by Nordenson.[12] Dameshek and Valentine[13] reported that the percentages of these abnormal cells varied roughly with the severity of the disease. Following therapy, these abnormal cells have been shown by Nordenson[12] and Scott[30] to disappear. Some authors—for instance, Doan and Zerfas,[34] Holmes and Broun,[35] and McLean[36]—have mentioned no such changes in the cells of the granular series. Tempka and Braun[39] and Nordenson[12] regarded these changes in the cells of the granular series as indicative of degeneration; but Jones[32][33][53] did not agree with that suggestion. Instead, he regarded them as representing processes in the maturation and development of a pathological neutrophilic series.

Tempka and Braun[39] found many naked megakaryocytic nuclei, and Jones[32] found that some of the megakaryocytes were intensely basophilic with a polymorphic nucleus and without granules in the cytoplasm. Dameshek and Valentine[13] found the megakaryocytes merely diminished in number, whereas Nordenson[12] held that they were normal. No agreement has yet been reached as to what changes, if any, occur in the megakaryocytes in pernicious anæmia.

Many of the macrocytic anæmias are supposed to be related to pernicious anæmia, in that they are thought to be due to some disturbance of the formation, absorption, storage or use of the hæmopoietic principle. Among the possible causes of such disturbances, the following may be listed: deficient intake of extrinsic factor (tropical and nutritional macrocytic anæmia, including the macrocytic anæmia of pellagra), decreased formation of intrinsic factor (gastric and intestinal resections), impaired absorption of the hæmopoietic principle (sprue, cœliac disease, worm infestations, Crohn's disease and intestinal anastomoses and ulceration), impaired storage and metabolism of the hæmopoietic principle in the liver (cirrhosis of the liver and possibly "pernicious anæmia" of pregnancy), and impaired utilization of the hæmopoietic principle in the liver (achrestic anæmia). A peripheral macrocytosis with a megaloblastic marrow has been rarely described in other diseases such as leuchæmia; but it is difficult to classify these findings in the above scheme of disordered metabolism of the hæmopoietic principle. Although macrocytosis and other changes in the peripheral blood have been reported in cases in which there is said to be a disordered metabolism of the hæmopoietic principle, very few reports have appeared with detailed descriptions of the accompanying changes in the marrow. These few reports will be briefly reviewed.

Weil and Perles[54] described as similar to that found in pernicious anæmia the marrow in cases of macrocytic anæmia associated with carcinoma of the stomach or with extensive intestinal resections. Wilkinson[37] had previously collected all cases of malignant disease associated with macrocytic anæmia which had been recorded up to 1933; he found that only 29 such cases had been reported. The situation of the primary growth was the stomach in 24 cases, the uterus in two and the kidney, pancreas and gall-bladder in the remaining three. To these Wilkinson[37] added a further six cases of his own of malignant disease associated with a macrocytic anæmia. In these cases the situation of the malignant growth was the mouth in three, the uterus in two and the stomach in one. Only in the last-mentioned case was the bone marrow examined, but no abnormality was detected. Merwe[48] examined the marrow in six cases of *carcinoma ventriculi*, four of which were associated with a macrocytic anæmia, but in all the marrow was normoblastic in type. Wilkinson[37] was also able to collect only twelve cases from the literature in which a macrocytic anæmia followed a previously performed gastrectomy. As far as can be ascertained, detailed examinations of the marrow were not made in these cases. In other cases in which a macrocytic anæmia has been reported associated with intestinal resections or anastomoses, the marrow has not been examined (Richardson,[55] Hurst,[56] Little, Zerfas and Trusler[57]), or the marrow when examined has been found to be normoblastic in type. McLean[36] has recently reported in this journal a case of macrocytic anæmia and megaloblastic marrow complicating extensive

gastro-intestinal ulceration, in which free hydrochloric acid was present in the gastric juice and in which there was no response to the exhibition of liver. The bone marrow in cases of macrocytic anæmia associated with sprue has been shown by Rhoads and Castle[61] to be megaloblastic before treatment; but with effective liver therapy the megaloblasts are replaced by normoblasts. Other reports of a megaloblastic marrow in sprue include those of Scott[20] and of Mackie and Fairley.[62] Scott[20] has also reported two cases of cœliac disease in which, associated with a macrocytic anæmia, there was a megaloblastic marrow. In both sprue and cœliac disease it appears that the marrow may be megaloblastic, normoblastic or aplastic. Macrocytic anæmia only infrequently accompanies infestation with *Bothriocephalus latus*; but in such cases Tottermann[63] has found megaloblastic bone marrow. A case of "pernicious anæmia" of pregnancy has been described by Heilbrun,[64] in which the marrow which had been megaloblastic changed to normoblastic within one month of the commencement of liver therapy. Israels[17] has also reported a case of "pernicious anæmia" of pregnancy, in which the marrow was megaloblastic in type. Tropical macrocytic anæmia has been shown by Wills[65] to respond to the exhibition of both liver and "Marmite", and one would therefore expect that the marrow would contain a predominance of megaloblasts. Fairley *et alii*,[66] working in Macedonia, have reported the occurrence of a nutritional macrocytic anæmia, in which the marrow presented a mixed megaloblastic and normoblastic erythropoiesis and presented similar changes in the cells of the granular series to those of pernicious anæmia. The only reference to megaloblastic marrow in tropical macrocytic anæmia appears to be that of Balfour;[67] but in his case post-mortem changes had occurred in the cells before examination.

Many reports have appeared of macrocytic anæmia associated with hepatic cirrhosis without detailed descriptions of the marrow (Wright,[68] Davidson and Fullerton,[69] Goldhamer,[70] Rosenberg,[71] Wintrobe and Shumacker,[72] and Duyn[73]). Israels and Wilkinson[74] stated that they had yet to encounter a case of macrocytic anæmia complicating liver disease in which the marrow was megaloblastic. Hynes[23] has reported the finding of normal marrow in a case of macrocytic anæmia associated with cirrhosis of the liver. Isaacs,[24] who regards the megaloblast as a normal stage in the production of the erythrocyte, present in the marrow in conditions other than pernicious anæmia and allied diseases, states that in uncomplicated cirrhosis of the liver the marrow resembles that of pernicious anæmia during relapse. It is not possible from his article, however, to determine how close he considers the resemblance to be. The macrocytosis associated with diseases of the liver and with jaundice is not accompanied by the poikilocytosis and anisocytosis of pernicious anæmia. At the moment the evidence indicates that Meulengracht's original belief that such macrocytosis is dependent upon chemical or physical alterations in the plasma, is correct. He suggested that the bile salts were the agents responsible for this change in the cells.

Achrestic anæmia of Wilkinson and Israels[74][75][76][77] resembles pernicious anæmia in that the anæmia is macrocytic and hyperchromic, and that the marrow is megaloblastic and contains "the curiously shaped metamyelocytes seen in pernicious anæmia". The chief differences between achrestic and pernicious anæmia are that in the former the liver contains the "antipernicious anæmia liver principle", the bone marrow remains partly megaloblastic despite liver therapy, free hydrochloric acid is present in the gastric juice, and there is a poor response in the general condition of the patient and in the peripheral blood to liver or stomach therapy. According to Israels and Wilkinson,[74] achrestic anæmia is "due to some interference with the proper action of the antipernicious anæmia liver principle on the erythropoietic tissues". Zanaty[78] has described four cases of aplastic anæmia, which he said were of the achrestic type; but his statement that the bone marrow in his cases was macroblastic would seem to indicate that the condition in these cases was aplastic anæmia and not achrestic anæmia as defined by Wikinson and Israels. Since Wilkinson and Israels's original description, sporadic reports of the marrow in achrestic anæmia by Hynes,[23] by Israels[17] and by Wauchope and Leslie-Smith[79] have appeared, confirming the presence of megaloblastic marrow in these patients.

Among the apparently unrelated cases in which the marrow has been described as megaloblastic are those of Israels and Wilkinson[77] (monocytic leuchæmia), of Dyke and Young[80] ("macrocytic hæmolytic anæmia with increased red cell fragility"), of Merwe[81] (generalized tuberculosis and macrocytic anæmia), and of McLean[82] (a case analogous to the "acute erythroblastic anæmia of childhood"). Megaloblasts have been described in the peripheral blood in Oroya fever by Fairley;[83] but I have been unable to find any reference to the marrow cells in that disease. Rarely, a macrocytic anæmia may be associated with acute rheumatic fever. Gwyn[84] has reported a case of acute rheumatic fever in which at autopsy the marrow was normoblastic in type. In one such case in which I had the opportunity to perform a sternal puncture the marrow was found to be normoblastic. No megaloblasts were seen and there was no evidence of the "giant stab forms".

On the experimental side, Wills and Stewart,[85] by means of a specially deficient diet, have produced a macrocytic anæmia in monkeys, in which they said the marrow (sections) showed a megaloblastic reaction; but it is likely that they were confusing pronormoblasts with megaloblasts, for their work has not been confirmed. Following the oral administration of liver to normal pigeons, Muller[86] studied the changes produced in the marrow. He also was apparently confusing megaloblasts with pronormoblasts in his sections, for Jones[87] was unable to find any cells of the megaloblastic series in marrow smears of normal pigeons. Stasney and Higgins[88] encountered atypical normoblasts, but found no true megaloblasts in the marrow of rats which developed cirrhosis of the liver and macrocytic anæmia following the inhalation of carbon tetrachloride.

It would appear that, as was to be expected, megaloblastic bone marrow has been described in cases of macrocytic anæmia due to some disturbance of the formation, absorption or use of the hæmopoietic principle. On the other hand, it has not been described in cases of macrocytic anæmia associated with disease of the liver, in which impaired storage of the hæmopoietic principle was postulated. The appearance of "giant stab forms" has been reported in the megaloblastic bone marrow associated only with pernicious anæmia, with achrestic anæmia and with nutritional macrocytic anæmia; but it is more likely that they have been overlooked in other diseases associated with megaloblastic marrow than that they were not present.

Apart from the articles by Scott[20] and Stodtmeister,[87] there has been practically no attempt in cases of hypochromic anæmia to follow the alterations in the marrow produced by iron therapy. By repeated sternal punctures Stodtmeister[87] has shown that in secondary hypochromic anæmia the reticulocytosis which follows the administration of iron is accompanied in the marrow by an increase in the erythroblasts, and that this increased percentage of the erythroblasts returns to normal when normality of the blood is reached. Scott[20] found that "in these cases there was a relative increase in the erythroblasts of the marrow roughly in proportion to the degree of the anæmia"; but he reported changes in some of the normoblasts to which he ascribed diagnostic significance. These characteristic normoblasts were said to be small and mature, with an irregular and jagged cell outline and only a small rim of slate-grey cytoplasm around the pyknotic nucleus. According to Scott,[20] no significant alteration occurred in the cells of the granular series. After iron therapy Scott[20] reported that the marrow returned to normal.

Method.

For diagnostic purposes I have previously expressed a preference for marrow specimens obtained by trephining of the sternum rather than specimens obtained by sternal

puncture;[88] but since repeated trephinings are impracticable, the specimens discussed in this article (except for those obtained *post mortem* in Case IV) were obtained by aspiration of the sternum. No anticoagulants were used. Approximately 0·2 millimetre of marrow and blood was aspirated; smears were made immediately, quickly dried in air and then stained as soon as possible by Leishman and May-Grünwald-Giemsa methods. Smears and sections were prepared from the marrow obtained at post-mortem examination in Case IV as previously described.[89] For the differential counts at least 1,000 cells were counted in the marrow smears and at least 200 cells in the smears of the peripheral blood.

Apart from the more mature cells of the marrow, for which there exists a generally acceptable, clear-cut nomenclature, the more primitive cells possess a somewhat confused nomenclature (as has already been mentioned), and therefore the terms used in this paper for the marrow cells of extrauterine life will be defined.

The promegaloblast (Figure I) is 12μ to 18μ in diameter. The nucleus is round and large, occupying at least two-thirds of the cell. As a whole, the nucleus has not the fine reticular appearance of the nucleus of the myeloblast. The chromatin strands and knots are slightly coarser, and scattered throughout the nucleus are a few larger chromatin clumps. The nucleoli, of which there are usually three or four, are small, ill-defined and surrounded by aggregations of chromatin. The nuclear membrane is poorly defined. The cytoplasm has a narrow, clear, perinuclear zone, which merges with a wider, non-granular basophilic zone in which numerous light areas produce a foamy appearance. At the periphery of the cell the cytoplasm is usually homogeneous and densely basophilic. Occasionally pseudopodia are present. The cytoplasm contains no hæmoglobin.

The basophilic megaloblast (Figure II) is 12μ to 16μ in diameter. The nucleus is round and large, occupying almost as much of the cell as in the promegaloblast. The nucleus has a more regular appearance than that of the promegaloblast, and no nucleoli are present. The chromatin network is slightly coarser; but the clumping of the chromatin, which is especially seen around the nucleoli of the promegaloblasts, is not present. The lighter areas of oxychromatin are more sharply defined than in the promegaloblasts. The nuclear membrane is poorly marked. The clear perinuclear zone of the cytoplasm is less sharply defined, while the foamy appearance may be more obvious than in the promegaloblasts. No pseudopodia are present. The cytoplasm contains no hæmoglobin.

The polychromatic megaloblast (Figure III) is 10μ to 14μ in diameter. The nucleus is round and occupies about half the cell. The chromatin is irregularly arranged in clumps, some larger than others, and with small but clearly defined light areas of oxychromatin between the clumps. The oxychromatin is not quite so sharply defined as in the corresponding cells of the definitive normoblastic series. No nucleoli are present. The nuclear membrane is clearly defined, and arranged around the inner side of this membrane are small clumps of chromatin. The clear perinuclear zone of the cytoplasm is poorly marked and may be absent. With the exception of a few clear areas, the cytoplasm is usually homogeneous. The cytoplasm stains to a slight degree with eosin, owing to the presence of hæmoglobin, and accordingly has a dusky, polychromatic appearance. The cytoplasm may contain one or more densely basophilic areas, quite distinct from the nucleus, resembling Howell Jolly bodies. The cell outline is round or oval.

The orthochromatic megaloblast (Figures IV and V) is 10μ to 14μ in diameter. The nucleus may be round, oval, lobulated or irregular, and occupies less than half the cell. The chromatin is arranged in large clumps, the edges of which are still not so sharply defined as in the corresponding cells of the definitive normoblastic series. The nuclear membrane is clearly marked. In the more mature cells the nucleus is pyknotic. The cytoplasm, except for the occasional presence of deeply basophilic areas resembling Howell Jolly bodies, contains its full complement of hæmoglobin and is homogeneous. The cell outline is usually irregularly oval in shape.

The pronormoblast (Figure VIII) is 12μ to 16μ in diameter. The nucleus is round, occupies about two-thirds of the cell and stains more deeply than that of the promegaloblast. The chromatin is arranged in slightly larger clumps than in the promegaloblast, and the areas of oxychromatin are more sharply defined in the pronormoblast. One or more ill-defined nucleoli surrounded by aggregations of chromatin are present. The nuclear membrane is better defined than in the promegaloblast. The clear perinuclear zone of the cytoplasm is usually smaller than in the promegaloblast. Throughout the remainder of the cytoplasm, which is deeply basophilic, there are numerous lightly staining areas producing a foamy appearance. The cytoplasm contains no hæmoglobin.

The early erythroblast is 8μ to 12μ in diameter. The nucleus occupies slightly less than two-thirds of the cell, and contains more heavily clumped chromatin than the pronormoblast. The areas of oxychromatin are sharply defined and resemble somewhat the fissures in dried clay. No nucleoli are present. The nuclear membrane is poorly marked. The cytoplasm is homogeneous and deeply basophilic. Rarely, in most severe anæmias, including pernicious anæmia, hæmoglobin may prematurely develop in the cytoplasm of this cell.

The late erythroblast is 8μ to 10μ in diameter. The nucleus is round and occupies about half the cell. The chromatin is arranged in large, dense clumps, which have started to fuse; but the clear areas of oxychromatin may still be easily seen. No nucleoli are present. The nuclear membrane is poorly marked. The cytoplasm is homogeneous and usually contains hæmoglobin; but the hæmoglobinization of the cytoplasm is most obvious in some cases of hæmolytic anæmia.

The normoblast is 6μ to 8μ in diameter. The nucleus is small and pyknotic, and is often eccentrically placed. The nucleus may be round, oval, lobulated or irregular in outline. A few densely basophilic areas may be present in the cytoplasm. These are presumed to be nuclear remnants. The cytoplasm is homogeneous and contains its full complement of hæmoglobin.

The term "erythrogone" is applied to cells 6μ to 8μ in diameter with a nucleus occupying most of the cell, and containing one or two nucleoli and a fine chromatin network, but not so fine as in the myeloblast. The narrow rim of cytoplasm is basophilic and homogeneous. Probably the majority of these cells are micromyeloblasts.

The myeloblast is 10μ to 12μ in diameter. The nucleus is round and occupies most of the cell. The chromatin is arranged in the form of a fine reticulum resembling a fine woven cloth. Two or three nucleoli are present, but there is no clumping of the chromatin around them. The nuclear membrane is poorly marked. The cytoplasm is small in amount and basophilic, and may contain azurophilic granules. There may be a narrow, incomplete, pale perinuclear zone in the cytoplasm. A few small pseudopodia of the cytoplasm may be present.

The premyelocyte is 10μ to 15μ in diameter. The nucleus occupies about two-thirds of the cell, and is round or slightly oval. The chromatin is more clumped than in the myeloblast, and remnants of nucleoli are present. The cytoplasm is much less basophilic than in the myeloblast, and contains, in addition to the azurophilic granules, a few type-specific granules.

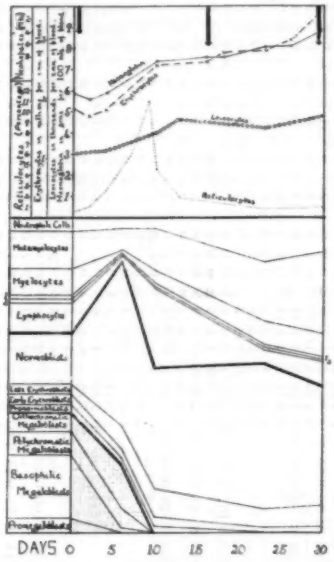
The myelocyte is 10μ to 14μ in diameter. The nucleus is round or oval and occupies about half the cell. The clumping of the chromatin is quite obvious, but it is arranged in a totally different manner from that of the megaloblastic or normoblastic series. Rarely, nucleolar remnants may be present. The cytoplasm contains many type-specific and a few azurophilic granules.

The young metamyelocyte is 8μ to 10μ in diameter. The nuclear chromatin is more dense than in the myelocyte. No nucleoli are present. The nucleus is oval or kidney-shaped and occupies about half the cell. The cytoplasm contains type-specific granules only.

The "giant stab forms" are 16μ to 18μ in diameter. The nucleus is deeply indented or tortuous and occupies about half the cell. The clumping of the chromatin resembles somewhat that of the myelocyte; but it may stain more lightly than in the latter cell. No nucleoli are present. Frequently there are one or more vacuoles in the nucleus. In the cells in which the vacuole is single and large, there is a superficial resemblance to some of the developing cells of the granular series in the rat. The cytoplasmic granules, the majority of which are type-specific, are usually finer than those of the myelocyte, but they may be coarser. The cell outline is round or oval. As Jones[53] pointed out, the cells appear to arise directly from the premyelocytes and to give rise to the macropolycytes of Cooke.

Reports of Cases.

CASE I.—K.R., a female patient, aged thirty-eight years had suffered from increasing weakness, dyspnœa on exertion and lassitude for six months, and from a feeling of "pins and needles" in the hands for one month. For many years she had suffered from vague epigastric discomfort irregularly related to meals, but this discomfort had not increased in intensity. She looked pale and had a slight icteric tinge of the conjunctivæ. The tongue was smooth and red. The examination of the nervous system revealed no abnormality. Neither spleen nor lymph glands were palpable. The tourniquet test produced a positive result. The Wassermann test failed to produce a reaction. The Van den Bergh test produced a weakly positive indirect reaction and the bilirubin level was 0·9 milligramme per 100 millilitres of plasma. Examination by means of an Ewald test meal revealed complete achlorhydria and increased mucus, but no blood in the gastric contents.



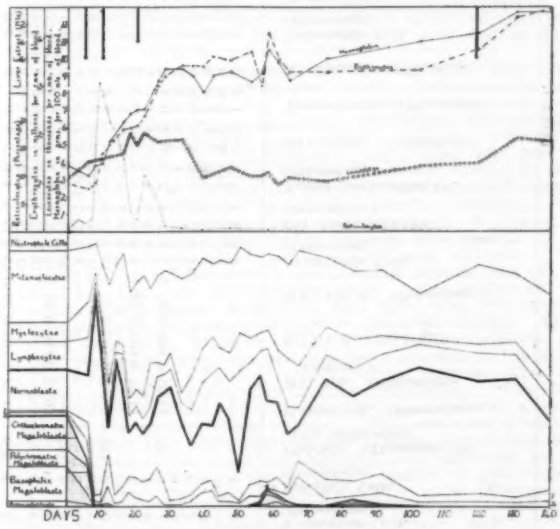
GRAPH I.

The upper set of graphs shows the changes in the hæmoglobin, the erythrocytes, the reticulocytes and the leucocytes of the peripheral blood before and after liver therapy in Case I. The lower set of graphs, a myelogram, shows the concurrent changes in the differential counts on the marrow smears before and after liver therapy. The whole ordinate of the myelogram is taken as representing 100% and then divided up, proportionate amounts being allotted to each type of marrow cell. Changes in the percentage of each cell are thus shown by variations in the width of the area representing that cell. In the myelogram the following cells have been grouped together: young and old metamyelocytes; pre-myelocytes and myeloblasts (1); eosinophile cells and basophile cells (2); and lymphocytes, plasma cells and monocytes. Mitotic figures, erythrogones and megakaryocytes have been omitted from the myelogram. The portion of the myelogram allotted to the megaloblastic series has been stippled. Thus, for example, it will be seen that by the tenth day the megaloblasts had completely disappeared from the marrow, that the myelocytes and lymphocytes had decreased in number, that the percentage of the pronormoblasts and early erythroblasts practically remained unaltered and that the percentages of late erythroblasts and normoblasts had both increased. The time and the amounts of the "Neohepatex" injections are shown by the arrows on the myelogram. In addition to the liver, three grains of ferrous sulphate were administered three times per day. Final diagnosis: pernicious anæmia.

The results of the examination of the blood and the bone marrow on the patient's admission to hospital and at intervals thereafter, and the time and amount of the liver injections given, are shown in Table I and Graph I. As a result of treatment, all her symptoms had disappeared by the time of her discharge from hospital five weeks after admission. In addition to the liver, three grains of ferrous sulphate were administered three times per day. The final diagnosis was pernicious anæmia.

CASE II.—S.A., a female patient, aged sixty-three years, who had previously enjoyed good health, had suffered from recurrent pain beneath the right costal margin, from dyspnœa on exertion, from œdema of the ankles, and from a feeling of "pins and needles" in the hands and feet for three months, and during this time she had lost a few pounds in weight. She looked pale and was distressed even at rest. The liver edge was palpable two fingers' breadth beneath the right costal margin, but no other abdominal mass or viscus was palpable. No lymph glands were palpable. The right knee jerk was slightly impaired, but no other abnormality of the nervous system was detected. An opaque meal examination revealed no abnormality in the stomach or duodenum. Examination by means of histamine and Ewald test meals revealed complete achlorhydria; but no blood or mucus was present in the gastric contents. The Van den Bergh test produced an indirect positive reaction, and the bilirubin level was 1·3 milligrammes per 100 millilitres of plasma. The basal metabolic rate was +1%.

The results of the examination of the blood and the bone marrow on the patient's admission to hospital and at intervals thereafter are contained in Table I and Graph II,



GRAPH II.

The upper set of graphs shows the changes in the hæmoglobin, the erythrocytes, the reticulocytes and the leucocytes of the peripheral blood before and after liver therapy in Case II. The lower set of graphs, a myelogram, shows the concurrent changes in the differential counts on the marrow smears before and after liver therapy. The whole ordinate of the myelogram is taken as representing 100% and then divided up, proportionate amounts being allotted to each type of marrow cell. In the myelogram the following types of cells have been grouped together: young and old metamyelocytes; myelocytes, pre-myelocytes and myeloblasts; lymphocytes, plasma cells, monocytes, histiocytes, eosinophile cells and basophile cells; and early erythroblasts and pronormoblasts (2). Late erythroblasts are represented by area (1). Mitotic figures, erythrogones and megakaryocytes have been omitted from the myelogram. The portion of the myelogram allotted to the megaloblastic series has been stippled. During the initial control period of five days three grains of ferrous sulphate were administered three times per day. The administration of iron was then discontinued until the one hundred and eighteenth day, when it was recommenced. Final diagnosis: pernicious aæmia.

TABLE I.

Blood.

Case Number.	Days.[1]	Hæmoglobin. (Grammes per Centum.)	Erythrocytes. (Millions per Cubic Millimetre.)	Colour Index.	Reticulocytes. (Percentage.)	Leucocytes. (Thousands per Cubic Millimetre.)	Neutrophile Cells. (Percentage.)	Lymphocytes. (Percentage.)	Monocytes. (Percentage.)	Eosinophile Cells. (Percentage.)	Basophile Cells. (Percentage.)	Platelets. (Thousands per Cubic Millimetre.)	Hæmatocrit. (Percentage.)	M.C. Hb. (Micromicrogrammes.)[2]	M.C. Vol. (Cubic μ.)[3]	M.C. Hb. C. (Percentage.)[4]
I	0	5·9	1·8	1·1	0·5	3·0	47	49	0	3	1	—	—	—	—	—
I	6	—	—	—	4·5	—	—	—	—	—	—	—	—	—	—	—
I	10	7·4	2·6	1·0	11·5	4·0	45	48	1	5	1	—	—	—	—	—
I	23	8·1	2·8	1·0	1·0	4·2	65	32	0	3	0	—	—	—	—	—
I	30	8·9	3·5	0·9	1·0	4·8	60	35	1	4	0	—	—	—	—	—
II	0	3·8	1·0	1·3	0·5	3·1	58	41	0	1	0	79	13	38·0	130·0	29·2
II	6	3·2	0·9	1·3	2·0	4·0	57	42	0	0	1	—	—	—	—	—
II	8	3·6	1·0	1·2	17·6	4·1	53	40	4	2	1	—	11	34·6	105·7	32·7
II	10	3·9	1·6	0·9	24·4	—	—	—	—	—	—	—	—	—	—	—
II	12	5·2	1·9	1·0	19·7	4·3	51	47	2	0	0	116	20	32·6	105·2	31·0
II	14	—	—	—	17·4	—	—	—	—	—	—	—	—	—	—	—
II	16	6·3	2·1	1·1	13·4	4·5	67	26	4	3	0	—	—	—	—	—
II	18	6·8	2·2	1·1	3·5	5·7	62	36	1	1	0	167	—	—	—	—
II	20	7·0	2·2	1·1	2·0	5·0	70	25	2	2	1	—	26	32·0	116·0	26·9
II	22	7·0	2·4	1·0	10·2	5·7	64	29	2	5	0	—	—	—	—	—
II	24	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II	26	8·7	3·0	1·0	5·2	5·3	55	30	5	9	1	319	31	28·3	103·0	29·0
II	28	9·4	3·2	1·0	1·2	—	—	—	—	—	—	—	—	—	—	—
II	30	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II	33	9·4	3·4	1·0	1·3	5·3	70	23	5	2	0	—	38	28·5	111·0	25·5
II	36	9·0	3·4	0·9	—	—	—	—	—	—	—	—	—	—	—	—
II	39	8·0	3·4	0·8	0·2	3·1	48	31	3	18	0	113	30	23·5	88·2	26·6
II	42	9·0	3·6	0·9	—	—	—	—	—	—	—	—	—	—	—	—
II	44	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II	47	9·2	3·5	0·9	0·8	3·7	38	34	7	21	0	87	32	26·2	91·4	28·7
II	50	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II	53	8·6	3·7	0·8	—	3·2	43	44	4	9	0	—	—	—	—	—
II	56	9·1	3·0	1·1	—	3·2	53	34	1	9	3	—	—	—	—	—
II	58	10·5	4·1	0·9	0·1	3·4	52	30	3	15	0	97	32	26·2	80·0	32·8
II	61	9·7	3·5	1·0	—	2·7	53	35	0	12	0	—	—	—	—	—
II	64	8·7	3·3	0·9	0·4	3·1	48	31	4	17	0	109	28	26·6	85·0	31·0
II	67	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II	75	10·0	3·3	1·1	—	2·9	—	—	—	—	—	—	—	—	—	—
II	83	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II	91	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II	102	11·0	3·3	1·2	0·3	3·8	62	30	3	5	0	116	36	32·8	107·4	30·5
II	119	11·5	3·9	1·1	—	4·0	65	32	0	8	0	—	—	—	—	—
II	130	12·7	4·5	1·1	—	5·4	53	42	2	3	0	—	40	28·2	88·0	31·7
II	140	12·7	4·6	1·0	0·5	5·2	59	38	0	3	0	—	—	—	—	—
III	0	5·1	1·5	1·2	1·0	6·1	73	25	2	0	0	—	18	35·3	120·0	34·0
III	1	5·0	1·5	1·2	—	5·9	69	30	1	0	0	—	—	—	—	—
III	2	5·6	1·6	1·3	—	6·5	72	22	3	3	0	—	—	—	—	—
III	3	6·0	1·6	1·5	2·2	7·0	58	32	3	7	0	—	—	—	—	—
III	4	6·2	1·8	1·2	—	8·9	69	25	1	5	0	—	—	—	—	—
III	5	6·5	2·0	1·2	12·9	6·9	70	27	0	3	0	—	—	—	—	—
III	7	6·6	2·2	1·1	5·4	8·5	61	29	2	7	1	—	—	—	—	—
III	25	9·4	3·2	1·1	1·4	8·4	75	19	2	4	0	—	—	—	—	—
IV	0	4·3	1·4	1·1	2·4	3·2	62	37	1	0	0	—	—	—	—	—
IV	2	4·2	1·3	1·1	1·9	3·8	65	34	0	1	0	98	13	32·3	100·0	32·3
IV	6	3·1	0·9	1·3	4·4	3·1	54	40	1	5	0	—	—	—	—	—
V	0	4·8	3·4	0·5	0·8	6·1	70	20	4	5	1	201	32	15·2	71·9	21·2
V	2	4·6	3·6	0·4	1·2	7·0	68	22	5	4	1	—	—	—	—	—
V	5	6·2	3·5	0·6	4·4	4·8	60	28	8	2	2	—	—	—	—	—
V	7	6·2	3·5	0·6	2·8	5·4	59	33	6	2	0	—	—	—	—	—
V	11	7·1	4·0	0·6	2·9	5·6	66	24	2	6	2	202	38	18·2	76·0	24·0
V	18	9·3	4·1	0·8	1·5	6·7	69	30	0	1	0	—	—	—	—	—
V	25	9·3	4·4	0·8	0·2	6·4	71	27	2	0	0	219	40	21·0	74·0	28·0
V	35	9·7	4·3	0·8	0·7	6·1	67	19	9	3	2	221	41	20·2	77·3	26·0

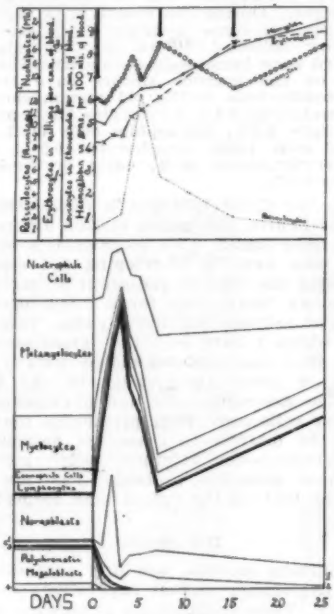
Bone Marrow.

Case Number.	Days.[1]	Neutrophile Cells. (Percentage.)	Old Metamyelocytes. (Percentage.)	Young Metamyelocytes. (Percentage.)	Myelocytes. (Percentage.)	Premyelocytes. (Percentage.)	Myeloblasts. (Percentage.)	Eosinophile Cells. (Percentage.)	Basophile Cells. (Percentage.)	Monocytes. (Percentage.)	Histiocytes. (Percentage.)	Plasma Cells. (Percentage.)	Lymphocytes. (Percentage.)	Normoblasts. (Percentage.)	Late Erythroblasts. (Percentage.)	Early Erythroblasts. (Percentage.)	Pronormoblasts. (Percentage.)	Orthochromatic Megaloblasts. (Percentage.)	Polychromatic Megaloblasts. (Percentage.)	Basophilic Megaloblasts. (Percentage.)	Promegaloblasts. (Percentage.)	Mitotic Figures. (Percentage.)	Ratio of Red to White Cells.	Megakaryocytes. (Percentage.)	Marrow Cell Count in Thousands per c.mm.[5]	Injection of Liver Extract. (Millilitres.)
I	0	4·2	8·4	3·3	8·3	1·4	0	1·2	0·4	0·4	0	1·0	7·7	17·3	3·2	3·4	2·6	6·0	8·6	19·2	4·8	0·6	1 to 0·52	0	—	4
I	6	3·6	4·8	2·0	1·2	0·8	0	0·7	0·1	0·4	0	0	21·6	52·1	7·7	2·7	2·0	12·3	6·4	1·2	0	0·4	1 to 0·18	0	—	—
I	10	3·5	8·6	5·0	3·9	1·0	0·1	0·8	0	0·1	0	0·2	4·9	39·1	8·7	3·2	1·8	0	0	0	0	0·1	1 to 0·89	0	—	6
I	23	14·4	11·5	7·3	6·8	0·8	0	1·3	0	0·2	0	0·4	4·5	44·6	6·4	2·0	0	0	0	0	0	0	1 to 0·89	0	—	—
I	30	11·2	20·2	5·1	7·3	0·4	0·2	0·9	0	0·1	0	0·4	7·5	37·9	6·7	2·3	0	0	0	0	0	0	1 to 1·0	0	—	6
II	0	7·1	23·4	2·3	6·2	0·4	0	2·7	0	0	0	0	6·6	14·9	0·4	0·1	0·7	12·6	6·1	14·6	1·9	0·3	1 to 0·96	0	183	—
II	6	5·4	16·4	4·5	10·4	1·7	0·2	2·5	0	0·4	0·1	0	9·7	17·2	6·8	6·7	0·2	1·9	9·6	6·0	0·2	0·1	1 to 1·0	0	163	6
II	8	4·4	7·6	2·5	2·6	0·1	0	1·8	0	0·4	0	0	0·8	78·1	1·5	0·1	0	0·1	0	0	0	0	1 to 0·25	0	200	—
II	10	12·4	18·7	4·3	3·0	0	0	1·4	0	1·2	0	0	5·8	49·9	2·6	0·4	0	0·2	0·1	0	0	0	1 to 0·88	0	98	6
II	12	19·8	28·6	6·3	11·7	0·4	0	1·5	0	0·1	0	0·2	0·8	10·6	11·4	6·5	1·2	0·6	0·5	0	0	0	1 to 2·2	0	60	—
II	14	11·7	20·2	8·2	2·8	0·1	0	0·3	0·1	0·2	0	0	1·2	51·1	3·2	0·5	0·1	0	0	0	0	0·3	1 to 0·82	0	96	—
II	16	8·2	23·7	10·1	2·2	0·5	0	0·6	0·2	2·0	0	0	9·1	36·3	5·2	1·3	0·5	0	0	0	0	0·1	1 to 1·3	0·1	98	—
II	18	22·4	32·5	6·4	6·1	0	0	4·1	0	0	0	0	1·6	16·2	5·5	4·2	1·0	0	0	0	0	0	1 to 2·7	0	41	—
II	20	18·6	32·2	7·3	5·0	0·9	0·2	1·7	0·3	0·7	0	0	2·7	19·3	7·1	2·1	1·2	0	0	0	0	0·3	1 to 2·3	0	37	4
II	22	16·1	27·7	15·7	7·3	0·5	0·4	3·6	0	0·2	0	1·1	1·5	16·6	6·7	2·2	0·4	0	0	0	0	0·1	1 to 2·8	0·1	58	—
II	24	21·0	22·0	4·2	14·2	2·0	0·1	3·0	0	0	0	0	3·0	20·2	7·8	1·7	0·6	0	0	0	0	0·2	1 to 2·3	0	26	—
II	26	15·9	27·5	4·0	5·5	0	0	3·2	0	0	0·1	0	3·0	26·2	10·6	4·0	0	0	0	0	0	0	1 to 2·5	0	56	—
II	28	14·1	30·2	4·1	3·2	0·1	0	2·4	0·1	0·1	0	0·2	3·3	33·2	8·1	0·9	0	0	0	0	0	0	1 to 1·4	0	67	—
II	30	17·6	22·9	6·0	5·3	0·6	0	3·9	0·3	0·1	0	0·1	1·8	39·5	1·4	0·3	0·2	0	0	0	0	0	1 to 1·4	0	74	—
II	33	17·5	31·7	9·7	3·6	0	0	3·7	0·1	0·4	0·1	0·2	1·7	28·8	2·1	0·3	0·1	0	0	0	0	0·1	1 to 2·2	0	53	—
II	36	15·7	31·2	5·4	11·0	0·5	0·9	6·4	0	0	0·3	0	6·0	16·2	2·7	0·3	1·2	0	0	0	0	0·2	1 to 3·9	0	45	—
II	39	10·1	25·1	7·4	13·5	1·4	0	6·7	0·2	0·6	0	0·1	7·4	18·9	3·2	3·4	1·6	0	0	0	0	0·4	1 to 2·7	0	69	—
II	42	11·6	22·1	4·1	10·2	3·2	0·4	7·9	0·6	0·7	0	0·4	9·3	20·4	3·6	2·7	2·4	0·3	0	0	0	0·1	1 to 2·4	0	58	—
II	44	10·9	24·9	6·2	7·4	0·2	0	7·1	0	0	0	0·2	5·1	34·7	1·3	1·0	0·6	0	0	0	0	0·3	1 to 1·6	0	40	—
II	47	11·3	26·0	6·7	10·0	0·9	0	7·7	0	0·2	0	0	5·1	25·9	3·5	1·3	0·3	0·5	0·2	0·2	0	0·2	1 to 2·1	0	39	—
II	50	5·6	26·2	4·0	12·2	1·0	0·4	9·6	0·2	0·8	3·0	0·4	23·0	11·6	0·6	0·8	0	0·6	0	0	0	0	1 to 7·1	0	92	—
II	53	8·4	25·1	4·9	8·5	0·2	0	4·3	0·1	0	0	0	5·2	35·2	4·1	3·9	0·1	0	0	0	0	0	1 to 1·4	0	57	—
II	56	9·1	20·3	6·1	6·4	0·2	0	3·4	0	0·1	0	0	4·5	41·2	5·4	2·2	0	0·5	0·1	0·5	0	0	1 to 1·0	0	25	—
II	58	7·8	22·2	5·2	5·5	0·9	0·1	7·5	0·1	1·5	0·1	0·2	9·5	30·7	2·3	0·1	0·5	0·5	3·8	1·2	0	0·3	1 to 1·5	0	27	—
II	61	9·4	29·3	4·2	10·6	0·4	0	2·1	0	0	0	0	5·3	29·0	4·2	1·4	0	1·8	1·8	0·5	0	0	1 to 1·6	0	35	—
II	64	12·4	24·2	9·8	17·3	0·1	0	3·4	0	0·1	0	0·3	4·7	21·3	2·1	2·8	0	1·2	0	0·3	0	0	1 to 2·6	0	73	—
II	67	6·5	37·2	4·5	14·0	0·1	1·0	6·0	0	0	0	0·4	0·4	14·3	5·2	8·0	2·1	0·2	0·1	0	0	0	1 to 2·3	0	49	—
II	75	9·3	19·4	5·3	9·6	0·4	0·1	4·2	0	0·1	0	0·3	3·5	37·9	6·5	3·4	0	0	0	0	0	0	1 to 1·1	0	27	—
II	83	14·3	19·5	5·3	10·6	0·2	0	3·4	0	0·1	0	0·2	6·4	30·9	5·4	1·3	0	1·2	0·7	0·5	0	0	1 to 1·5	0	39	—
II	91	14·0	21·0	3·0	6·7	0	0	2·1	0·6	0·1	0	0·1	6·8	33·2	6·7	2·2	2·2	0·6	0	0	0	0·8	1 to 1·2	0	48	—
II	102	22·5	13·4	3·8	2·1	0·1	0	3·1	0·1	0·3	0·3	0	4·3	46·8	2·1	0·8	0·3	0	0	0	0	0	1 to 0·99	0	37	—
II	119	12·4	24·2	4·1	3·2	0·4	0	4·2	0	0·2	0·4	0	5·2	40·6	3·1	2·0	0	0	0	0	0	0	1 to 1·1	0	38	—
II	130	15·5	22·1	2·2	4·5	0·2	0	2·3	0	0·5	0	0	5·4	43·6	2·4	1·3	0	0	0	0	0	0	1 to 1·1	0	48	—
II	140	23·1	26·5	4·9	4·9	0·5	0	2·0	0·4	0·6	0·2	0·2	4·8	26·2	3·5	1·7	0·1	0·1	0	0	0	0·3	1 to 2·1	0·2	54	—
III	0	17·4	26·9	6·2	14·4	0·8	0·1	5·3	0	0	0·2	0	3·2	12·4	0·3	0·8	0	0·7	9·3	1·7	0·1	0·2	1 to 3·0	0	—	10
III	1	16·5	15·4	3·2	8·5	0·1	0	3·4	0	0	0	0	4·5	37·1	4·5	2·7	0·1	2·7	2·2	0·1	0	0	1 to 1·1	0	—	—
III	2	3·7	15·0	5·1	4·3	0	0	2·8	0	0	0	0·5	1·0	33·9	27·6	2·8	0	1·2	0·8	0	0	0·5	1 to 0·49	0	—	—
III	3	1·6	9·5	1·8	1·8	0	0	2·3	0	0	0	0	1·4	75·3	2·9	2·2	0	0·7	0	0	0	0·5	1 to 0·23	0	—	—
III	4	9·8	14·2	3·1	5·4	0·1	0	5·2	0	0·1	0	0·2	3·4	48·8	4·2	5·0	0·5	0	0	0	0	0	1 to 0·73	0	—	—
III	5	10·9	19·2	4·5	6·9	0	0	2·5	0	0·4	0	0·1	3·4	42·4	4·8	4·9	0	0	0	0	0	0	1 to 0·92	0·1	—	—
III	7	27·7	26·1	6·8	5·4	0	0	4·1	0	0	0	0·5	0·6	17·1	7·8	3·2	0·7	0	0	0	0	0	1 to 2·5	0	—	4
III	25	24·9	12·1	4·5	3·0	0	0	3·3	0	0	0	0	3·2	43·0	5·8	0·2	0	0	0	0	0	0	1 to 1·0	0	—	4
IV	0	3·2	16·4	4·3	14·5	0·2	0	2·1	0	0·2	0·4	0·3	3·4	23·1	5·4	2·1	0·7	2·3	13·5	7·4	0	0·5	1 to 0·83	0	—	12
IV	2	5·0	4·9	12·1	13·4	0·1	0	3·4	0	0·1	0	0·2	2·0	33·1	2·2	1·2	0	13·2	3·9	4·3	0·6	0·3	1 to 0·70	0	—	—
IV	6	0·4	5·4	2·4	23·6	0·7	0·1	1·1	0·1	0	0·1	0·2	6·0	46·1	0·5	1·1	0	6·0	2·7	1·3	1·7	0·5	1 to 0·67	0	—	—
V	0	20·5	12·3	1·5	8·9	0·1	0	2·7	0	0·4	0	0	1·1	28·4	18·0	4·2	1·3	0	0	0	0	0·6	1 to 0·90	0	—	—
V	2	8·0	13·4	3·2	5·5	1·3	0	2·2	0	0	0	0·1	0·1	34·3	17·4	10·1	3·4	0	0	0	0	1·0	1 to 0·51	0·1	—	—
V	5	12·3	18·4	7·1	3·4	0·2	0	3·1	0	0·2	0	0·3	3·4	27·7	15·5	7·3	0·8	0	0	0	0	0·2	1 to 0·94	0	—	—
V	7	18·2	18·1	5·4	5·0	0·8	0	3·2	0	0·2	0	0·4	2·0	35·6	7·1	2·8	1·0	0	0	0	0	0·2	1 to 1·1	0	—	—
V	11	12·4	21·3	3·1	4·2	0·2	0	3·9	0	0·1	0	0·3	2·5	43·9	5·4	1·9	0·8	0	0	0	0	0	1 to 0·92	0	—	—
V	18	16·2	30·1	3·3	2·5	0·3	0	2·7	0	0·1	0	0·2	2·0	34·0	6·7	0·5	0·8	0	0	0	0	0	1 to 1·3	0	—	—
V	25	28·3	23·2	3·7	5·1	0·3	0	4·2	0	0·3	0	0	5·4	24·1	4·6	0·6	0·2	0	0	0	0	0	1 to 1·9	0	—	—
V	35	6·0	39·6	5·3	11·2	0·8	0	5·4	0	0	0	1·0	0·9	22·0	3·0	2·8	1·1	0	0	0	0	0	1 to 2·4	0	—	—

[1] Days counted from the day of admission to hospital. [2] Mean corpuscular hæmoglobin. [3] Mean corpuscular volume. [4] Mean corpuscular hæmoglobin concentration. [5] Counted on the fluid aspirated from the sternum.

as are also the time and amount of the liver injections ("Neohepatex" and "Anahæmin"). During the initial control period of five days she was given ferrous sulphate (three grains three times per day), but no liver. After the control period she was given intramuscular injections of liver and no iron for four months. Thereafter she was given both liver and iron. Within a month of the onset of treatment with liver all her symptoms had disappeared and her knee jerks were normal. The result of a hippuric acid liver function test (Quick) was then 97% of normal. The final diagnosis was pernicious anæmia.

CASE III.—A.B., a female patient, aged seventy-four years, had, according to her daughter, suffered from dyspnœa on exertion, from weakness, from œdema of the ankles and from mental confusion for two weeks and from persistent vomiting for two days. Two years previously she had a similar attack, which was diagnosed as due to pernicious anæmia; she was then treated with blood transfusions and "Anahæmin". During this original attack her hæmoglobin value increased from 2·8 to 9·0 grammes per 100 millilitres of blood in six weeks. For the next twelve months she had attended hospital regularly for injections of "Neohepatex", and examination of her blood repeatedly revealed a hæmoglobin value above 12·5 grammes per 100 millilitres. During the past year, however, she had not attended hospital for treatment.



GRAPH III.

The upper set of graphs shows the changes in the hæmoglobin, the erythrocytes, the reticulocytes and the leucocytes of the peripheral blood before and after liver therapy in Case III. The lower set of graphs, a myelogram, shows the concurrent changes in the differential counts on the marrow smears before and after liver therapy. The whole ordinate of the myelogram is taken as representing 100% and then divided up, proportionate amounts being allotted to each type of marrow cell. In the myelogram the following types of cells have been grouped together: young and old metamyelocytes; myelocytes, premyelocytes and myeloblasts; eosinophile cells and basophile cells; lymphocytes, plasma cells and monocytes; and early erythroblasts and pronormoblasts (2). Late erythroblasts are represented by area (1), orthochromatic megaloblasts by area (3), and promegaloblasts by area (4). Mitotic figures and megakaryocytes have been omitted from the myelogram. The portion of the myelogram allotted to the megaloblastic series has been stippled. In addition to the liver, three grains of ferrous sulphate were administered three times per day. Final diagnosis: pernicious anæmia.

On examination the patient was very obese and very pale. The tongue was smooth and red. Examination of the nervous system revealed a stumbling gait, hyperæsthesia to pin-prick, and absence of knee and ankle jerks. The Wassermann test produced no reaction. The Van den Bergh test produced an indirect reaction, and the bilirubin level was 0·8 milligramme per 100 millilitres of plasma. Examination by means of an Ewald test meal revealed complete achlorhydria; but no blood or mucus was present in the gastric contents. Table I and Graph III contain the results of the examination of the blood and bone marrow on the patient's admission to hospital and at intervals thereafter, and also the time and amount of the liver injections. Two millilitres of "Benerva" were also given every third day, three grains of ferrous sulphate were given three times per day, and one drachm of dilute hydrochloric acid was given with meals. The final diagnosis was pernicious anæmia and probable early subacute combined degeneration of the spinal cord.

CASE IV.—J.C., a male patient, aged fifty-six years, had suffered from increasing dysphagia for twelve months and from weakness and dyspnœa on exertion for six months. During these six months he had lost five stone in weight, and on examination of the patient this loss in weight was quite obvious. The skin and mucous membranes were very pale. The Wassermann test produced no reaction. The blood urea content was 54 milligrammes per 100 millilitres of blood.

Four days after the patient's admission to hospital a Thorek gastrostomy operation was performed, but death from bronchopneumonia occurred two days later. Portions of the liver and gastric mucosa were removed at operation; Dr. F. B. Byrom's reports on these specimens were as follows:

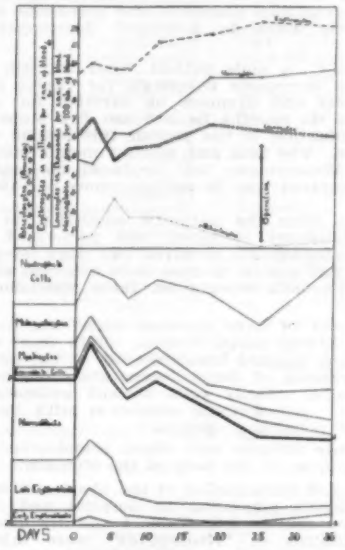
> Fragment of liver showing slight fibrous thickening of capsule and portal strands, slight focal round-celled infiltration, marked hæmosiderosis of the periphery and some evidence of fatty degeneration of the centre of the lobules. Many cells showed evidence of stored glycogen. Appearances consistent with but not diagnostic of pernicious anæmia.
>
> Moderate atrophy and slight round-celled infiltration of the mucosa of the body of the stomach.

The results of examination of the blood and bone marrow on the patient's admission to hospital and at intervals thereafter are contained in Table I and are discussed later. Twelve millilitres of "Neohepatex" were injected intramuscularly on the day after his admission to hospital, but were without effect. Stomach contents aspirated just prior to death contained no free hydrochloric acid and no blood or mucus.

At autopsy five centimetres of the œsophagus were found to be almost occluded by a firm, warty, carcinomatous ulcer encircling the lumen; but I was unable to find any peri-œsophageal adhesions or malignant infiltration. The proximal part of the œsophagus was slightly dilated. Pneumonic consolidation of the lower lobes of both lungs was present, and the left pleural cavity contained several ounces of clear yellow fluid. The mediastinal lymph glands appeared normal. The recent gastrostomy wound was healing normally. The stomach was normal in size and contained 20 ounces of thin, whitish fluid. The gastric mucosa was smooth in the fundus, but corrugated in the body and pylorus. The omentum was adherent to the healing suture line of the stomach and the gastrostomy tube. The walls of the jejunum and ileum were thin and pale, and the mucosa was atrophic. The large intestine appeared normal. There were no streaky deposits of fat in the subpericardium, and only slight atheromatous changes were present in the aorta. The spleen was enlarged (weight, seven ounces), firm and dark, and had prominent fibrous trabeculæ. The liver weighed 56 ounces, and the cut surface presented a much darker appearance than normal. The sternum contained red marrow; but fatty marrow was present throughout both femora and tibiæ. No abnormality was detected in the suprarenals, kidneys, ureters, urinary bladder or gall-bladder. The body was that of a cachectic, elderly male. Microscopic examination revealed solid acinar columnar-celled and polygonal-celled carcinoma of the lower end of the œsophagus, focal chronic inflammatory infiltration of the mucosa of the body and pylorus of the stomach, active hæmopoiesis of the marrow of the sternum with a predominance of promegaloblasts and megaloblasts and with very few megakaryocytes, and fatty aplastic marrow from the femur. The final diagnosis was carcinoma of the œsophagus with slight atrophy of the mucosa of the stomach and the small bowel and megalocytic anæmia.

CASE V.—E.C., a male patient, aged forty-nine years, had suffered from tiredness, from tachycardia and from dyspnœa on exertion for five years. For two months he had suffered from pain in the anal region and from bleeding immediately after defæcation. He was obese and pale. Large internal hæmorrhoids, which bled easily, were present. Sigmoidoscopic examination revealed no other abnormality. The barium enema flowed without obstruction around to the caecum, and no filling defect or other abnormality could be

detected. The results of examination of the blood and bone marrow on the patient's admission to hospital and at intervals thereafter are contained in Table I and Graph IV. The patient was given three grains of ferrous sulphate three times per day for two days and then six grains three times per day. Hæmorrhoidectomy was performed under spinal anæsthesia and convalescence was uneventful. The final diagnosis was bleeding internal hæmorrhoids and secondary hypochromic anæmia due to chronic blood loss.



GRAPH IV.

The upper set of graphs shows the changes in the hæmoglobin, the erythrocytes, the reticulocytes and the leucocytes of the peripheral blood before and after iron therapy in Case V. The lower set of graphs, a myelogram, shows the concurrent changes in the differential counts on the marrow smears before and after the administration of iron. The whole ordinate of the myelogram is taken as representing 100% and then divided up, proportionate amounts being allotted to each type of marrow cell. In the myelogram the following cells have been grouped together: young and old metamyelocytes; myelocytes, premyelocytes and myeloblasts; eosinophile cells and basophile cells; lymphocytes, plasma cells and monocytes (1). Pronormoblasts are represented by area (2). Mitotic figures and megakaryocytes have been omitted from the myelogram. Hæmorrhoidectomy was performed on the twenty-fifth day after the patient's admission to hospital. Final diagnosis: internal hæmorrhoids and chronic blood loss; secondary hypochromic anæmia.

CASE VI.—A male patient, aged fifty-eight years, had for two years suffered from weakness of the legs, and this had become progressively worse for the past fourteen weeks. During these fourteen weks he had also suffered from a feeling of "pins and needles" in the hands and feet, and once, twelve weeks before his admission to hospital, he had temporarily lost control of micturition. His tongue was smoother than normal. Both legs were slightly spastic, impairment of power being greater in the left leg than in the right. The knee and ankle jerks were absent and the Babinski plantar reflex was elicited in both feet. Hyperalgesia affecting the distribution of the fourth and fifth lumbar nerves, and impaired appreciation of pain and temperature, but not of touch, in the distribution of the first sacral nerves were present. Position sense was slightly impaired. The optic disks were normal, and no other abnormality was found on clinical examination. X-ray examination of the thoracic and lumbar vertebræ revealed spondylitis. The cerebro-spinal fluid was clear and colourless and contained 209 lymphocytes per cubic millimetre, an amount in excess of the number usually present in subacute combined degeneration of the cord. The Wassermann test produced no reaction with the blood or the cerebro-spinal fluid. A second specimen of cerebro-spinal fluid contained 90 milligrammes of glucose, 716 milligrammes of sodium chloride and 76 milligrammes of protein per 100 millilitres. On this occasion the number of leucocytes in the cerebro-spinal fluid was not increased. The Lange colloidal gold test produced a negative result. The increase in the protein content may have been due on this occasion to slight contamination of the fluid with blood. An Ewald test meal examination revealed complete achlorhydria and increased mucus, but no blood, in the gastric contents.

On the patient's admission to hospital the examination of the blood revealed that the hæmoglobin value was 92% (12·9 grammes per 100 millilitres), the erythrocytes numbered 5,120,000 per cubic millimetre, the colour index was 0·9 and the leucocytes numbered 10,000 per cubic millimetre. A differential leucocyte count gave the following results: neutrophile cells 61%, lymphocytes 30%, monocytes 4% and eosinophile cells 5%. Some of the red cells were larger than normal. The neutrophile cells showed a pronounced shift to the right.

In addition to liver injections the patient was given three grains of ferrous sulphate three times per day and two millilitres of "Benerva" per day. No reticulocytosis followed liver therapy (20 millilitres of "Campolon" given twice a week). Two weeks after the commencement of treatment examination of his blood revealed that the hæmoglobin value was 92% (12·9 grammes per 100 millilitres), the erythrocytes numbered 4,560,000 per cubic millimetre, the colour index was 1·01, the hæmatocrit value was 46%, the mean corpuscular hæmoglobin content was 29·1 micromicrogrammes, the mean corpuscular hæmoglobin concentration was 29·1%, and the mean corpuscular volume was 100 cubic microns. Some of the erythrocytes were again larger than normal, and the neutrophile cells still showed a pronounced shift to the right. During the month spent by the patient in hospital there was some lessening of the spasticity. The sternal marrow collected before the beginning of liver therapy showed some increase in cellularity. The differential count made on the marrow smears gave the following result: neutrophile cells 15·7%, old metamyelocytes 24·8%, young metamyelocytes 8·4%, myelocytes 5·1%, premyelocytes 0·9%, myeloblasts 0·3%, eosinophile cells 5·1%, monocytes 0·1%, plasma cells 1·2%, lymphocytes 0·5%, normoblasts 36·3%, late erythroblasts 1·0%, early erythroblasts 0·2%, mitotic figures 0·4%.

Apart from the slight increase in the plasma cells and in the mitotic figures, the result of this differential count is within normal limits. No megaloblasts or pronormoblasts were seen and the developing red cells appeared normal. Among the cells of the granular series, however, there were many "giant stab forms", macropolycytes and hypersegmented polymorphonuclear cells. This is the only occasion on which I have seen the "giant stab forms" in the marrow in a case not associated with a macrocytic anæmia due to some abnormality of the hæmopoietic principle. The macropolycytes and hypersegmented polymorphonuclear cells have been previously found in small numbers in the marrow in cases not associated with a macrocytic anæmia—for example, acute infections—and therefore their presence probably has not the same significance as that of the "giant stab forms".

Discussion.

When pernicious anæmia was first separated from the other blood dyscrasias, various suggestions were made as to its ætiology. These included the suggestion of a relationship to the leuchæmias and the suggestion that the underlying factor was one of excessive blood destruction. With the introduction of liver therapy and the demonstration that it resulted in a change from megaloblastic to normoblastic marrow, Peabody[9] put forward the theory of an arrest of maturation of the developing red cells. The discovery by Castle and co-workers of the hæmopoietic principle was regarded as further evidence in favour of this theory; the hæmopoietic principle, or a substance formed from it, was thought to be the missing factor necessary for the further maturation of the megaloblast. While the existence of the hæmopoietic principle has not been seriously questioned, doubt has been cast on the manner in which a deficiency of the hæmopoietic principle affects the bone marrow. Tempka and Braun[20] were the first to make the important observation that changes are present in the developing cells of the granular series and in the megakaryocytes of the bone marrow of pernicious anæmia during relapse; but they made the probably erroneous assumption that these changes were degenerative in origin. Since then, Jones[10][11] has demonstrated changes in the developing cells of the granular series and in the megakaryocytes of pernicious anæmia during relapse; but he and Nordenson[12] regarded these changes,

ILLUSTRATIONS TO THE ARTICLE BY DR. T. E. WILSON.

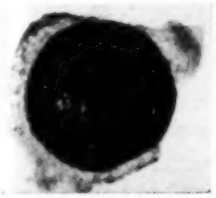


FIGURE I.

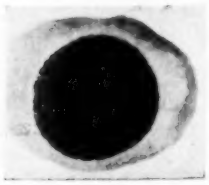


FIGURE II.

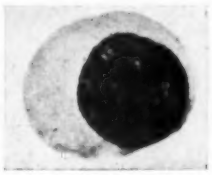


FIGURE III.

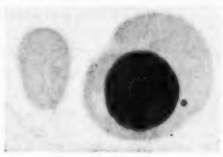


FIGURE IV.

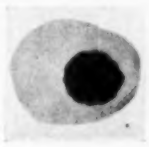


FIGURE V.

Figures I to V show the typical stages of the megaloblastic series present in marrow smears in Case II before liver therapy. The magnification in Figures I to IX is approximately 1,200 diameters. Figure I, promegaloblast; Figure II, basophilic megaloblast; Figure III, polychromatic megaloblast; Figure IV, orthochromatic megaloblast and erythrocyte; Figure V, orthochromatic megaloblast with more pyknotic nucleus than Figure IV.

FIGURE VI.

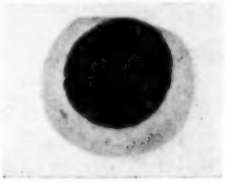


FIGURE VII.

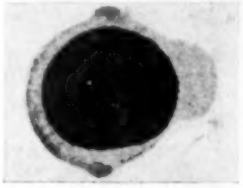


FIGURE VIII.

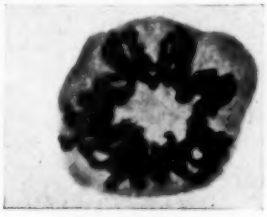


FIGURE IX.

Figure VI: Primitive erythroblast from liver smear of 12-millimetre embryo. The nucleus bears some resemblance to that of Figure I, but the two cells are not identical. Figure VII: Primitive erythroblast from the liver of a 40-millimetre embryo. This cell was indistinguishable from some of the pronormoblasts in Case V. Figure VIII: One of the most primitive pronormoblasts seen in the marrow smears in Case V. The similarity of this cell and the promegaloblast of Figure I is apparent, but again the two are not identical. Figure IX: Basophilic megaloblast in mitosis (metaphase), Case III.

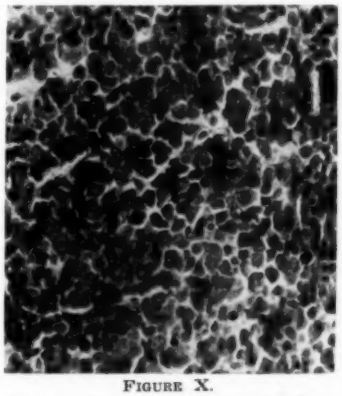


FIGURE X.

Section of sternal marrow in Case IV. Magnification approximately 300 diameters.

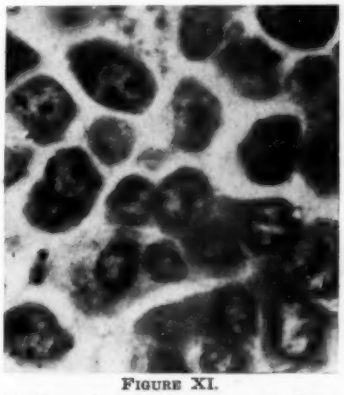


FIGURE XI.

Section of sternal marrow in Case IV, showing a group of megaloblasts. Magnification approximately 1,000 diameters.

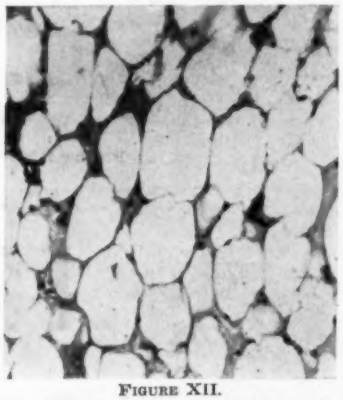


FIGURE XII.

Section of the femoral marrow in Case IV, showing the absence of the hyperplasia usually seen in the femoral marrow in pernicious anæmia.

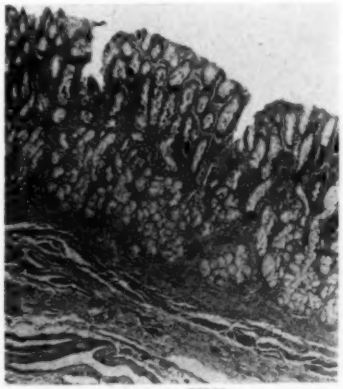


FIGURE XIII.

Section of the gastric mucosa in Case IV, showing a moderate degree of atrophy and slight, small, round-celled infiltration.

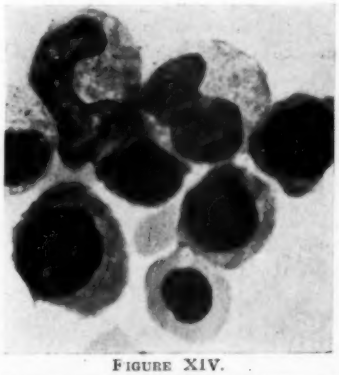


FIGURE XIV.

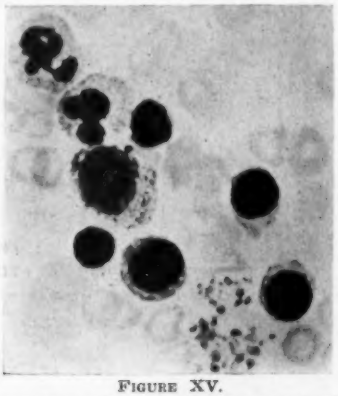


FIGURE XV.

Marrow smears in Case II before and three days after the commencement of liver therapy. Figure XIV shows two "giant stab forms" and several megaloblasts. In Figure XV the normoblasts, the late erythroblast, the normal cells of the granular series and the platelets may be seen.

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FIGURE III.

FIGURE IV.

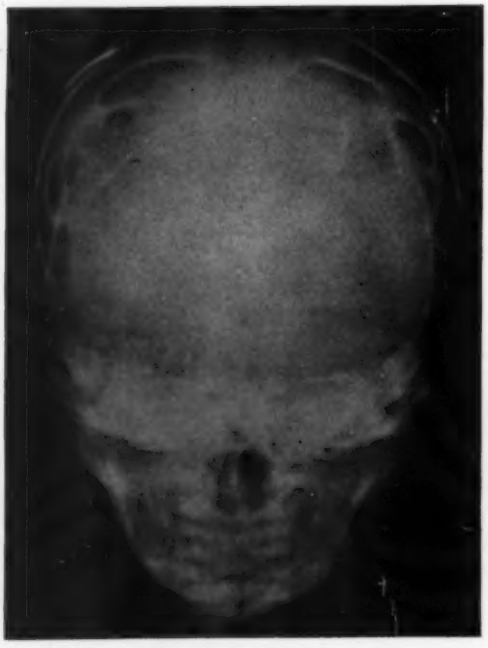

FIGURE V.

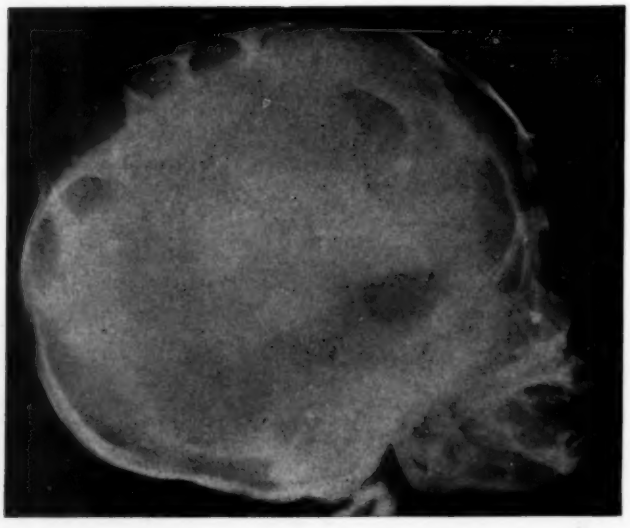

FIGURE VI.

not as degenerative, but rather as evidence of the development of an abnormal series of cells. Jones[52][53] also regarded the megaloblastic series as abnormal, and he introduced the concept of a panmyelopathy in pernicious anæmia. On this basis, the hæmopoietic principle may be considered as preventing development of these abnormal series of cells while stimulating and allowing the ordinary development—that is, definitive normoblastic erythropoiesis and myelopoiesis—to proceed.

Recently the theory that the hyperplastic marrow in pernicious anæmia is a response to excessive blood destruction has been revived by Dobriner and Rhoads,[49] who have in support of this theory shown that the pigment metabolism in pernicious anæmia, untreated or in relapse, resembles that of the hæmolytic anæmias, but returns to normal in a remission. These authors suggest that the hæmopoietic principle produces its effect mainly by diminishing the rate of blood destruction. The low reticulocyte count of pernicious anæmia, untreated or in relapse, is the chief evidence against excessive blood destruction and regeneration in this disease; but it has been suggested by Rhoads that the reticulocytes may be destroyed before they enter the circulation.

In an attempt to throw some light on the mode of action of the hæmopoietic principle, it was decided to follow at frequent intervals the changes produced in the marrow of a patient with pernicious anæmia but without subacute combined degeneration of the cord (Case II), first, in a therapeutically induced remission, and then if possible during the early development of a relapse. Over a period of ten weeks 27 sternal punctures were performed, and then seven more in the next ten weeks. Two other patients with pernicious anæmia in relapse, on whom this procedure was attempted, were not so long-suffering, and fewer punctures were possible. In a case of carcinoma of the œsophagus associated with megalocytic anæmia, the death of the patient cut short the serial marrow examinations. In Case V, one of chronic blood loss, the changes occurring in the marrow coincident with improvement in the blood condition following iron therapy are interesting, but do not seem to help greatly in the correlation of the unexplained facts of pernicious anæmia. Case VI is described, for as far as can be determined there exist no descriptions of the marrow in cases of subacute combined degeneration of the cord unassociated with pernicious anæmia. Such descriptions are important, for they may illustrate the early development of megaloblastic marrow. A difficulty arises in Case VI, however, for although the bone marrow was abnormal, the diagnosis of subacute combined degeneration of the cord, while probable, was by no means proved. No other cause for the abnormality of the marrow could be found; but caution is necessary in the application of conclusions drawn from this bone marrow to that in pernicious anæmia.

The marrow in pernicious anæmia, untreated or in relapse, is hyperplastic, and there is no lack of proliferation of the promegaloblasts and megaloblasts. Whether the promegaloblast develops from the reticulum cells, from an undifferentiated stem cell or from the pronormoblast, is undecided; but it cannot materialize from nothing. Its development, from whatever cell it proceeds, is completely inhibited in association with normal metabolism of the hæmopoietic principle; but if from any cause the metabolism of the hæmopoietic principle is abnormal, this inhibition fails and megaloblastic erythropoiesis ensues. Similarly the hæmopoietic principle probably inhibits the development of the abnormal cells of the granular series of pernicious anæmia. These abnormal cells of the granular series have, as already mentioned, no counterpart in the embryo, and although their presence does not necessarily disprove the theory that the megaloblastic erythropoiesis of pernicious anæmia is a reversion to an embryonic type, it is perhaps reasonable to assume that if erythropoiesis had returned to an embryonic level, the development of the other marrow cells would have done the same. The orthochromatic megaloblasts of the early embryo may, apart from their more regular outline, be indistinguishable from the orthochromatic megaloblasts in pernicious anæmia; but the ancestral cells (primitive erythroblasts) from which these hæmoglobinized forms have developed in the embryo are not identical with the promegaloblasts or basophilic megaloblasts in pernicious anæmia (*vide* Figures I and VI). (Ehrlich did not recognize a non-hæmoglobinized megaloblast.) On the other hand, erythropoiesis in the older embryo very closely resembles that seen in adults in conditions in which erythropoiesis is stimulated (Figure VII). "Toxic" granulation of the neutrophile cells and macropolycytes have been described (Wilson[60]) in the marrow during acute infections, and these cells are apparently identical with similar cells present in the marrow in pernicious anæmia; but with the exception of Case VI, I have not seen the "giant stab forms" in the marrow in acute infections or in any other diseases except those associated with disordered metabolism of the hæmopoietic principle. It may be concluded that the hæmopoietic principle normally inhibits the development of the "giant stab forms". There are, however, in the marrow in pernicious anæmia, many less cells of the "giant stab form" than megaloblasts. In my specimens the only definite abnormalities that have been observed with regard to the megakaryocytes in pernicious anæmia (untreated, in relapse or in remission), have been their infrequent occurrence and their decreased lobulation. If the platelets are formed from the megakaryocytes, then their reduction in number is probably quite sufficient to account for the thrombocytopenia of this disease without the postulation of any abnormality of the megakaryocytes. The presence in pernicious anæmia, untreated or in relapse, of a few pronormoblasts in the marrow in addition to the promegaloblasts and megaloblasts, would seem to indicate the possible formation of small amounts of the hæmopoietic principle in the body or the incomplete exhaustion of the stores of the hæmopoietic principle even at death. These are only suggestions, and there is no direct evidence in support of either. Still, the fact that some of the cells of the granular series are unaffected in pernicious anæmia, untreated or in relapse, may also indicate that some hæmopoietic principle is available.

After the commencement of liver therapy more mature cells of the megaloblastic series appear in the marrow, while pronormoblasts, early and late erythroblasts and especially normoblasts, rapidly increase in number. These cells of the definitive normoblastic series must have developed from cells already present in the bone marrow before the liver therapy was begun—that is, either from cells of the megaloblastic series or from the pronormoblasts. After treatment with liver there is little increase in the pronormoblasts in the marrow; but it is probable that many of those pronormoblasts originally present have rapidly proliferated and produced numerous erythroblasts and normoblasts. Because cells of the megaloblastic series are only present in the marrow in conditions associated with interference with the metabolism of the hæmopoietic principle, it does not necessarily follow, as has been assumed in the past, that a megaloblastic to normoblastic transformation is impossible. The great increase in the normoblasts of the marrow soon after the onset of liver therapy without any appreciable alteration in the percentages of the later or early erythroblasts, as in Cases I and II, and then subsequently their reduction to normal numbers with the continuation of the liver therapy, may be interpreted as indicating partly that there is a sudden stimulation of the pronormoblasts (directly or by the removal of an inhibiting factor) which is not sustained when treatment is continued, and partly that the rapid but temporary increase of the normoblasts, or cells resembling normoblasts, is the result of their development from the megaloblasts which are now enabled to ripen without further reproducing their kind. This latter suggestion would to some extent explain the decrease in the normoblasts when treatment is continued, for erythropoiesis is then proceeding along normal lines at a normal rate, and the supply of megaloblasts would be soon exhausted. The reticulocytosis associated with liver therapy follows within a day or two this appearance of such large numbers of normoblasts in the marrow—that

is, it coincides with the decrease again in the percentage of normoblasts. Thus the normoblasts, or cells resembling normoblasts, which have suddenly appeared in the marrow after the exhibition of liver, are capable of development to reticulocytes. Following the disappearance of the megaloblasts from the marrow there is an increase in the percentages of the early and late erythroblasts, as the marrow continues to respond to the stimulus of the anæmia. In Case II no significant change in the marrow was seen associated with the second reticulocyte peak. The great increase in the late erythroblasts in Case III on the second day after the commencement of the liver therapy was not seen in Cases I and II. Yet, if after liver therapy there is a sudden but temporary stimulation of the few pronormoblasts present in the marrow in pernicious anæmia, untreated or in relapse, one would have expected an increase in the early and late erythroblasts coincident with the sudden increase in the normoblasts.

In Case II the megaloblasts had completely disappeared from the marrow within eight days of the commencement of liver therapy; but they did not reappear for thirty-six days after the third liver injection. The first cells to reappear were not promegaloblasts, hæmocytoblasts or other primitive cells, but instead orthrochromatic and polychromatic megaloblasts. No intermediate stages between these megaloblasts or other cells of the megaloblastic series and pronormoblasts, myeloblasts or reticulum cells were found in the marrow at or before the time of reappearance of the megaloblasts. From a study of the marrow smears at this stage no evidence as to the origin of the megaloblastic series could be uncovered, and it is considered that probably a few cells of the megaloblastic series persist in the marrow during a remission in numbers so few that they may be absent from aspirated material. The variations in the percentages of the megaloblasts between the sixtieth and hundredth days in Case II may be attributed to the fact that during this time the patient began to take small amounts of liver by mouth.

The large number of lymphocytes present in the marrow in Case II on the fiftieth day was probably due to aspiration near a lymph node.

The "giant stab forms" had vanished from the marrow in Case II by the eighteenth day, but they were subsequently found in the majority of the marrow specimens examined throughout the remainder of the period of observation in this case. In Case I the "giant stab forms" had disappeared from the marrow by the twenty-third day, and in Case III by the twenty-fifth day. Thus the "giant stab forms" are not so rapidly affected by the hæmopoietic principle as the megaloblasts. In Case VI the "giant stab forms" may indicate the initial alteration of the marrow in early pernicious anæmia; but since there was some doubt as to the diagnosis in this case this suggestion is by no means proved.

One of the unusual features in Case IV was the association of a megalocytic anæmia with a carcinoma of the œsophagus. (I have been unable to find a report of a similar case in the literature.) Complete achlorhydria was present, and although the gastric mucosa was slightly atrophic and showed some evidence of a chronic inflammatory reaction (Figure XIII), there was not the extreme degree of atrophy usually seen in pernicious anæmia. The hyperplastic marrow did not extend throughout the bones of the lower limb. Unfortunately, the bones of the upper limbs were not examined. Such a failure of the hyperplastic marrow to extend throughout the long bones is an infrequent but well recognized occurrence in pernicious anæmia. It may, in this case, indicate a recent origin of the anæmia. Before the commencement of treatment the sternal marrow in this case was typical of untreated pernicious anæmia; but the poor response to a potent liver preparation is probably explained by the low-grade pulmonary infection. After the liver injection changes were discernible in the marrow, consisting of a decrease in the megaloblasts and an increase in the normoblasts; but these changes were not of the same order as in successfully treated pernicious anæmia and were apparently insufficient to produce any appreciable change in the peripheral blood.

Before the onset of treatment in Cases I, II and III, the late erythroblasts contained very little hæmoglobin and the early erythroblasts none; but within three weeks of the commencement of liver therapy in each case the cytoplasm of the late erythroblasts contained more than their normal complement of hæmoglobin, and many of the early erythroblasts contained some hæmoglobin.

Immediately after the administration of iron was begun in Case V, the first change observed in the marrow was an increase in the percentage of the early erythroblasts and pronormoblasts. This had occurred by the second day; but thereafter with the gradual improvement in the peripheral blood the percentages of the early and late erythroblasts and pronormoblasts decreased. At no stage were abnormal cells seen in the marrow in this case. The effect of the iron appears to be one of stimulation of the pronormoblasts, early and late erythroblasts and normoblasts, rather than that of supplying a maturation factor for any one stage of erythropoiesis. One of the most primitive red cells found in the marrow specimens in Case V is shown in Figure VIII. The denser arrangement of the chromatin is usually sufficient to distinguish such cells from the promegaloblasts of pernicious anæmia. The pronormoblasts bear less resemblance to the primitive erythroblasts of the early embryo (Figure VI); but pronormoblasts which are slightly more mature than the cell shown in Figure VIII may appear identical with the primitive erythroblasts of older embryos (Figure VII). Although the promegaloblasts of pernicious anæmia have been identified with the primitive erythroblasts of the early embryo by some hæmatologists and with the pronormoblasts of extrauterine life by other hæmatologists, neither school failed to distinguish between the primitive erythroblasts of the early embryo and the pronormoblast of extrauterine life.

Summary and Conclusions.

1. The literature on the terminology of the cells of the blood and of the bone marrow in pernicious anæmia, in secondary hypochromic anæmia and in conditions in which the marrow is megaloblastic, is reviewed.

2. Serial marrow examinations are described in two cases of pernicious anæmia during relapse and during early remissions, in one case of pernicious anæmia before treatment, during remission and later during an early relapse, in one case of a carcinoma of the œsophagus and megalocytic anæmia, and in one case of hypochromic anæmia secondary to chronic blood loss during the response to therapy with iron. The marrow is also described in a probable case of subacute combined degeneration of the cord not associated with pernicious anæmia.

3. It is concluded that after liver therapy in pernicious anæmia ripening of the abnormal megaloblasts occurs, but without the development of further megaloblasts, and that there occur an initial temporary stimulation and then later a lesser, but more prolonged, stimulation of the definitive normoblastic cells. The abnormal cells of the granular series present in pernicious anæmia are not comparable with any embryonic cells, nor does the megaloblastic series of pernicious anæmia represent a reversion to embryonic erythropoiesis. The hæmopoietic principle may be regarded as inhibiting the development of the abnormal megaloblasts and "giant stab forms" while stimulating normal development of the cells of the red and white series. From the study of the marrow in pernicious anæmia during an early relapse, no evidence could be adduced as to the origin of the megaloblasts, and it is concluded that the reappearance of the megaloblasts during an early relapse is due to megaloblasts which have persisted in the marrow in numbers too few to be detected in aspirated material. After liver therapy in pernicious anæmia the "giant stab forms" decrease more slowly than the megaloblasts, so that for some time after the first week of treatment they remain the only diagnostic feature in the marrow. The megakaryocytes are reduced in number in pernicious anæmia, untreated, during relapse

or during remission; but a decreased lobulation of the nuclei was the only abnormality seen in these cells.

4. Since the only abnormality seen in the marrow in a probable case of subacute combined degeneration of the cord not associated with pernicious anæmia were the "giant stab forms", these may represent the initial change in the marrow in pernicious anæmia; but as the diagnosis in this case is still in doubt, this suggestion is not proved.

5. By the second day after the administration of iron in a case of secondary hypochromic anæmia, examination of the marrow revealed an increase in the percentage of the early erythroblasts and pronormoblasts, but thereafter the percentage of the early and late erythroblasts and pronormoblasts decreased. The administration of iron rather stimulates all stages of the definitive red cell series instead of supplying a maturation factor for any one stage of erythropoiesis. The cells of the definitive red cell series are the only primitive red cells common to the marrow in pernicious anæmia and in secondary hypochromic anæmia.

Acknowledgement.

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CONGENITAL LACUNAR SKULL ("LÜCKENSCHÄDEL").

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THE term *Lückenschädel* is used not only in the German but also in the British and American literature to designate a peculiar condition of the skull occasionally observed in new-born children. The term was apparently coined by Engstler[(1)] in 1905, but the condition itself has been known for a much longer period. It is characterized by defects in the vault, which vary considerably in size, shape and number. They occur in the form of shallow depressions or deep cavitations and penetrate often right through the bone until only a parchment-like membrane consisting of dura and periosteum is left. Frequently these membranes bulge slightly outwards. The defects lined by smooth, thick ridges of bone are most commonly seen in the frontal and parietal bones, but occur also in the occipital region; frequently their arrangement corresponds to the configuration of the brain surface. The condition is practically always associated with some kind of disturbance of occlusion of the medullary canal, mostly in the form of a *spina bifida* with meningocele.

West[(2)] (1875) is often credited with having reported the first case of this kind; but, according to Wieland, much earlier reports, dating back to 1771, can be found in the literature on forensic medicine. One year before West, Hofmann[(3)] had already published a very comprehensive study of the subject. Two short reports by White[(4)] and Goodhart[(5)] followed West's publication. Von Recklinghausen[(6)] (1886) in his work on *spina bifida* drew our attention for the first time to the combination of these two conditions. About twenty years later interest in the subject was revived by a paper by Heubner,[(7)] two years later followed Engstler's publication, and in 1909 Wieland[(8)] published a comprehensive review of the literature, added a number of his own cases and gave a complete analysis of all the aspects of the condition. His paper is the fundamental work on which all later discussion is based.

The first report in the American literature is that by Markoe[(9)] in 1907; but this was not followed until twenty-five years later by a few additional publications—for example, by those of Kerr,[(10)] Dorrance,[(11)] Doub and Danzer,[(12)] and Maier.[(13)] In 1936 Rothbart[(14)] published a comprehensive study of the subject. In the meantime, M. B. Schmidt[(15)] (1910) had given a short report of the condition under the term "Relief Skull", and in 1913 Kato[(16)] had published M. B. Schmidt's cases in detail. One of the most important papers on the subject is that by Faust[(17)] (1931); apart from adding a large number of new cases, he dealt extensively with the question of the development of the condition.

Before I enter into a discussion of the problems concerned, a full description of the condition will be given, as no such case had yet been published in the Australian literature, and only one further report, a very brief publication by Shearer[(18)] (1934), seems to have appeared in British journals since 1886.

The description is based on a case which has recently come under observation at the Women's Hospital, Melbourne.

Mrs. E.B., aged twenty years, was delivered of her first baby after a pregnancy which had been uneventful, but terminated prematurely at the end of the eighth month. The child was a female weighing 2,550 grammes. On examination a *spina bifida* of the lumbar region and both feet in extreme talipes position were seen. The child lived for seven days. During this time a steadily increasing tension of the fontanelle was present, the temperature was of the swinging variety, and signs of inflammation of the *spina bifida* were noted.

At post-mortem examination the organs of the chest and the abdomen were normal except for the presence of a horseshoe kidney. Pathological changes of the skeleton concerned the feet, the vertebral column and the skull.

Both feet were in extreme talipes position. In the lumbar vertebræ not only were the non-united arches of the *spina bifida* seen, but also a peculiar sharp-angled kyphosis in this region, for which no satisfactory explanation could be found. The most striking changes, however, were to be seen in the skull.

After removal of the galea, a large number of slightly bulging areas were found. They were covered only by a thin membrane with no bone. A number of them were of a slightly oblong shape, being symmetrically arranged to both sides of the mid-line in the parietal bones, their long diameter lying in a transverse direction. Further, such areas were seen in the frontal and occipital bones, here arranged in a somewhat more irregular way. After removal of the vault the areas presented themselves from the inside as deep cavitations lined by thick, smooth ridges of bone. On the surface of the brain pronounced, only slightly flattened convolutions were seen, and a good correspondence between the most prominent gyri and the bony defects was noticeable. After removal of the brain a gross exaggeration of the configuration of the basis of the skull could be seen. All the grooves were deeper and all the ridges more prominent than usual, but the condition was not so advanced as in the vault. A horizontal section through the brain revealed a considerable hydrocephalus.

The findings are illustrated in the figures. Figure I shows the skull from above after removal of the galea. A few bulging areas can be clearly seen. Figure II is a view of the vault from the inside. The numerous defects, their arrangement and their lining by thick ridges of bone are noticeable. Figure III is a picture of the vault taken by transillumination. It shows best the extent of the defects and the complete resorption of bone in these areas. Figure IV shows the exaggeration of the configuration of the basis of the skull. Figures V and VI are taken from the series of skiagrams. Figure VII shows the shape of the face of the baby, which will be discussed later on.

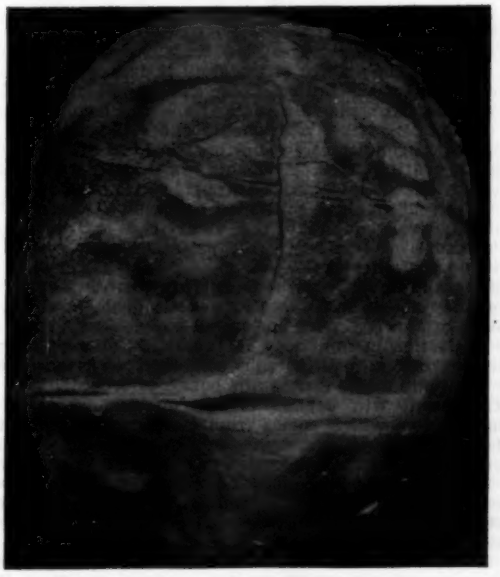

FIGURE I.

The X-ray findings are so typical that Maier was able to make the diagnosis from films taken some time before delivery. They bear a certain resemblance to two conditions only, and these can usually be excluded quite easily. First, in cases of extreme increase of the intracranial pressure, usually by tumours, an exaggeration of the normal digitations may lead to somewhat similar X-ray appearances; but the resemblance is only a superficial one, and the general findings in most cases will lead to the right diagnosis. Secondly, there may be some resemblance to the "geographical skull" of Schüller-Christian's disease. In this condition, however, the outline of the defects is never so smooth, their distribution is quite irregular, and the age of the patient and his general condition will again enable the correct diagnosis to be made.

FIGURE II.

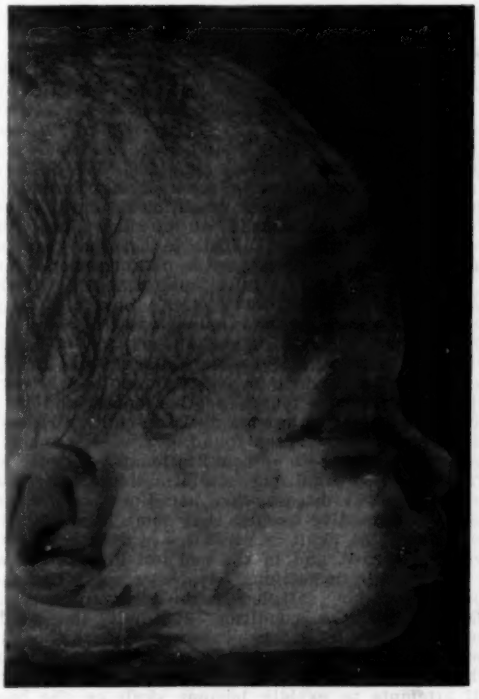

FIGURE VII.

Pathogenesis.

The pathogenesis of lacunar skull has been a matter of much speculation. In the early days it was mainly considered to be a manifestation of rickets. Although

Wieland disposed of such ideas, he created new confusion by regarding lacunar skull as a sub-group of a much more common condition which he called *Weichschädel* (soft skull). *Weichschädel* is according to him caused by an incongruity between the growth of the skull and of the brain during the last months of pregnancy. As during this period the brain grows very rapidly, the apposition of new bone cannot keep pace with this rate of growth, and a disproportion between the fibrous and the osseous cranium results. This manifests itself clinically by wide fontanelles, gaping sutures, serration and softness of the sutures, and softness and brittleness of the parietal bones. In Wieland's series, such a condition was observed in about 20% of the cases. It was his opinion that in addition to these defects of apposition, defects by resorption developed when the incongruity between brain and skull growth became even more pronounced and the intracranial pressure thus increased still more. The typical lacunar skull was therefore to him only the most severe form of the much more common *Weichschädel*. He recognized the association of lacunar skull with *spina bifida*, but its significance lay for him only in its increasing intracranial pressure.

It was soon seen that this conception was wrong. The typical lacunar skull is an entity of its own; therefore all the later publications concentrated on this particular condition. M. B. Schmidt and Kato in particular stressed this point. They agreed with Wieland's conception of the *Weichschädel*, but disagreed with his interpretation of the lacunar skull. In their opinion the latter condition is closely coordinated with *spina bifida*, although they were not able to show what kind of relationship existed between them.

In more recent years discussion has mainly centred around three questions: (i) Is lacunar skull a manifestation of a general disease? (ii) Is it a disturbance of the local ossification process? (iii) Is it due to intracranial pressure, and if so, what is the mechanism responsible for it?

The idea that lacunar skull was a manifestation of a general disease has been advanced by Hughes.[3] Nutritional or infectious diseases, such as rickets or syphilis, are in his opinion likely causes of the condition; but his own cases lend very little support to such a suggestion, and all the histological examinations by earlier or later writers disprove this idea. The observation of multiple malformations in cases of lacunar skull has led to the suggestion that the condition is nothing but one malformation amongst others, all of them being due to some genetic disturbance. This is certainly erroneous. Lacunar skull is the result of a malformation—namely, the *spina bifida*—but not a malformation in itself. Otherwise it would have been observed without simultaneous occurrence of a *spina bifida*. Lacunar skull is furthermore not a manifestation of a systemic deficiency of ossification. In cases like the one presented, in which the whole skeleton was examined by X rays, no similar changes were found in other bones, and in cases associated with systemic bone diseases nothing resembling lacunar skull has ever been found. Vague statements that such infants belong to a constitutionally inferior group characterized by multiple malformations and lowered resistance against disease, that hereditary or endogenous factors are causative agents, that some kind of primary hypostosis of the skull is present, are equally difficult to prove or disprove, and in the end not helpful. It seems that many such suggestions have been made because the authors were not satisfied with a purely mechanical explanation of the condition and felt the need for some other factor in the causation of the condition. Whether this point of view is correct may be seen in the further discussion.

All attempts to explain lacunar skull on the basis of a primary disturbance of the local ossification processes are confronted with two main difficulties. First, general disturbances of ossification are quite well known, but with regard to strictly localized disturbances we are without parallel occurrences in other parts of the skeleton, nor do we know of any primary condition which would lead to such a local disturbance. Secondly, histological examination has shown that the defects are largely due to resorption of bone—that is, that the defects are secondary changes in normally ossified bone.

It has therefore been suggested that intracranial pressure may play a part, but that it can manifest itself in this particular way only when some deficiency of ossification is present. This is said to be due either to some hypothetical primary constitutional hypostosis (see above) or to a nutritional deficiency of the skull caused by ischæmia (Rothbart); but this in turn would be again caused by intracranial pressure. It can therefore be seen that intracranial pressure seems to be an indispensable factor in the causation of lacunar skull. Whether it can be considered to be the sole agent or the main factor within a certain group is perhaps of secondary importance.

Before I enter into a discussion of this problem, it may be mentioned that some authors have thought that pressure from without may be a causative agent. Pressure of the pelvic brim against the fœtal head was considered amongst the ætiological factors; but this line of reasoning had to be abandoned as soon as cases of lacunar skull were observed after breech presentation. In a discussion of the significance of intracranial pressure as cause of lacunar skull, care must be taken to fit into the picture the *spina bifida*, as cases do not occur in the absence of this or a corresponding malformation. This is a point which has not received the necessary attention by all the authors whose suggestions were discussed with regard to the first two ætiological questions. On the other hand, changes which result from an operative interference with the *spina bifida* or from an infection of it, ought to be carefully excluded. The lacunar skull is present before birth, as Maier has proved. Therefore the hydrocephalus which often develops after surgical removal of the *spina bifida* or meningitis cannot be regarded amongst the likely causes of the condition, although it increases the intracranial pressure.

The starting point for all deliberations will have to be the fact that the growth of the skull is dependent upon the development of the brain. Loeschcke and Weinnoldt have shown this in extensive investigations and have elucidated all the details of this relationship under physiological and pathological conditions. Faust has reported an interesting case illustrating this relationship: in a skull with a large defect in the occipital bone through which practically the whole cerebrum had prolapsed, a vault had not been formed at all, so that the skull had an animal-like architecture. Nevertheless the parietal bones showed the features of "relief skull".

Skull and brain grow during the greater part of the pregnancy at the same rate. Towards term, however, the growth of the brain is accelerated to such an extent that the apposition of new bone in the skull cannot keep pace with this rate of growth; thus some disproportion between the cranium and its contents is bound to occur.

The result will depend mainly on the extent of the disproportion, which varies from case to case. If it is of a lesser degree, changes will not be noticeable. Higher degrees of such disproportion will manifest themselves as Wieland's *Weichschädel*. Lacunar skull cannot result, because the cerebro-spinal fluid forms a kind of water cushion around the brain, and any pressure exerted on the inside of the skull will be equal throughout, as Weinnoldt[10] has shown. In cases of *spina bifida* a different mechanism will develop, and we owe it to Faust to have first directed attention to it. When a *spina bifida* is present, the cerebro-spinal fluid can give way to the growing brain by escaping into the meningocele, and the subarachnoidal space is thus depleted of it. The convolutions of the brain therefore come into close contact with the inner table of the vault. When, then, the disproportion between the growth of the brain and the skull reaches a certain degree, resorption defects of the bone will be produced wherever the gyri press most closely against it.

Rothbart, in discussing this mechanism, has raised the objection that "it is difficult to picture such a pliable and plastic structure as the brain producing erosions in the less pliable skull without undergoing morphological

changes". In raising such an objection he overlooked the fact that the brain is not only a soft, pliable structure, but also a pulsating organ. We know well the far-reaching effects of a continuous pulsation against non-yielding structures. The destruction of vertebræ, ribs and other bones by aortic aneurysms amply illustrates the old truth: *"Gutta cavat lapidem."*

Another objection against this interpretation has been that increase of the intracranial pressure ought to manifest itself in bulging fontanelles and sutures rather than in rarefaction of bone; bulging fontanelles, however, are not commonly found in this condition. In such statements no account is taken of the fact that the fœtal skull is surrounded by the amniotic fluid. This fluid mantle will obviate any pressure differences and thus prevent fontanelles and sutures from bulging.

The presence or absence of the amniotic fluid furthermore provides an explanation for some other observations; in some cases bulging of fontanelles and lacunæ is seen, but when proper attention is paid to it it is noticed that this develops and increases after birth—that is, in the absence of a counter pressure by the amniotic fluid.

Absence of the amniotic fluid also accounts for the fact that lacunar skull never develops after birth. In extrauterine life intracranial pressure can and does lead to bulging fontanelles and sutures rather than to an erosion of bone.

Another objection against the explanation presented has been raised by authors who actually found changes in the blood vessels in the neighbourhood of the lacunæ. This seemed in their opinion to point towards a local causation of lacunar skull. Loeschcke and Weinnoldt, however, have shown that pressure atrophy occurs by means of impairment of the local blood supply and thereby the nutrition. Therefore such changes are but manifestations of the general process as outlined above.

This theory has a decided advantage; it invokes only one pathological factor, the altered hydrodynamics in the presence of a meningocele. All the other necessary factors of the mechanism are provided by physiological processes, such as the difference in the rate of growth of brain and skull, the pressure exerted on to the skull from within and without. It is unnecessary to resort to a range of hypothetical factors, such as constitutional inferiority or hereditary or endogenous disturbances, although it may not be possible completely to deny that they provide the background on which the condition develops.

Conclusions.

The mechanism leading to the development of lacunar skull can now be summarized as follows. Towards the end of pregnancy occurs a physiological incongruity between skull and brain. Under normal conditions localized effects are not possible, because the cerebro-spinal fluid, acting like a water cushion, ensures an equal pressure on all parts of the cranium. In cases of meningocele, however, the cerebro-spinal fluid will escape into the sac and the brain will thus come into direct contact with the inner surface of the vault. Additional space for the growing brain cannot be obtained by bulging of the non-osseous parts of the cranium, because the amniotic fluid around the skull obviates all pressure differences. Erosion of the bone by pressure atrophy will therefore occur wherever the gyri press most closely against the inner table. A typical lacunar skull will thus develop.

This interpretation does not require the introduction of constitutional factors in the pathogenesis. Nevertheless, there is a possibility that some kind of constitutional abnormality is present in such infants. The frequent occurrence of multiple malformations points in this direction. Faust has furthermore drawn attention to a peculiar physiognomy of many of these infants. They often have a rather senile looking face. The root of the nose, as Figure VII shows, is deeply drawn in, with a resultant sharp angle between the forehead and the ridge of the nose. Whatever the significance of such factors, they certainly do no more than provide the background on which lacunar skull develops.

Summary.

1. The history of lacunar skull (*Lückenschädel*) is briefly reviewed.
2. A full description of the condition is given on the basis of the observation of a typical case.
3. The pathogenesis is discussed, and from the many theories advanced Faust's suggestions are held to have paved the way for a reasonable explanation of the condition.
4. Objections against this interpretation are discussed and rejected.

Acknowledgement.

I wish to thank Dr. Colin Macdonald for the skiagrams.

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Reports of Cases.

MENINGITIS FOLLOWING ACUTE OTITIS MEDIA TREATED WITH SULPHAPYRIDINE.

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I CONSIDER the following case history of interest, in that the early symptoms and signs of meningitis were masked by sulphapyridine therapy, and that the meningitis was secondary to acute *otitis media*, although at the time the

meningitis was apparent the *otitis media* had resolved and the ear drums were normal. The organism was not isolated from the cerebro-spinal fluid on repeated attempts at culture, but was presumably one of the pyogenic cocci.

Clinical Record.

Robert R., aged six and a half years, was a twin child of poor physique. His previous history included recurrent tonsillitis, recurrent otorrhœa, pertussis, varicella, scarlet fever, bronchopneumonia and rickets.

The child was first examined on May 10, 1941; he had bilateral otorrhœa of one week's duration. His temperature was normal, and he had no pain and felt well. On May 16 he complained of headache and of pain in the right ear. On examination he was found to have a temperature of 100·4° F. and a pulse rate of 120 per minute; the right ear was discharging freely and slight tenderness was present over the right mastoid region. The left ear had ceased to discharge. Sulphapyridine ("M & B 693") was given in a dose of one tablet (0·5 gramme) every four hours. The aural discharge rapidly cleared up, although the temperature remained about 99·2° F. and the pulse rate 80 to 90 per minute.

On May 19 the child still felt ill and complained of headache and anorexia. His abdomen was sunken and wasting was obvious, although he had vomited only twice during the illness and had taken some food. Slight neck rigidity was present; but no head retraction and no spine sign was noted, and Kernig's sign was not elicited. Both ear drums were healed and appeared normal. The right mastoid region was no longer tender. The patient was admitted to the Royal Alexandra Hospital for Children.

On his admission to hospital on May 19 lumbar puncture yielded opalescent cerebro-spinal fluid under increased pressure. There were 455 cells per cubic millimetre, of which 76% were polymorphonuclear cells and 24% lymphocytes. Glucose was present, the globulin test produced a positive result, and the chloride content of the fluid was 750 milligrammes per 100 cubic centimetres. A clot formed containing fibrin and polymorphonuclear cells. No organisms were detected on a smear or grown on attempted culture. A blood count gave the following information: the erythrocytes numbered 3,840,000 per cubic millimetre, the hæmoglobin value was 11·4 grammes, and the leucocytes numbered 9,200 per cubic millimetre. Of the leucocytes, 71% were polymorphonuclear cells, 24% were lymphocytes and 5% were monocytes.

The dosage of sulphapyridine was increased to two tablets (1·0 gramme) every four hours, and an alkaline mixture was given. The child's temperature on his admission to hospital was 101·4° F. and his pulse rate was 88 per minute. The temperature fell rapidly to normal and then rose again. After May 24 it showed slight daily elevations to 99·5° F. and reached normal on May 29. The same dosage of sulphapyridine was continued for a further week, when hæmaturia occurred and treatment was suspended. The hæmaturia cleared up rapidly.

Altogether four lumbar punctures were carried out. The number of cells in the cerebro-spinal fluid was highest on May 23—2,150 cells per cubic millimetre. No organisms were grown at any time on attempted culture. The number of erythrocytes in the blood fell to 3,720,000 per cubic millimetre and the hæmoglobin value to 8·7 grammes (50%); but rapid recovery occurred after the suspension of sulphapyridine therapy. An X-ray examination of the mastoid regions on May 30 revealed "no definite lesion".

On June 14 the child's temperature rose again and the left ear discharged pus; but the trouble cleared up after a few days. On June 26 an operation for the removal of tonsils and adenoids was performed by Dr. Ramsay Beavis. Convalescence was uneventful and the patient returned home on July 5.

Reviews.

THE STORY OF MATTHEW FLINDERS.

IN a novel bearing the not very satisfactory title "My Love Must Wait", Ernestine Hill has told the story of Captain Matthew Flinders, R.N., and has told it so well that Australians of every generation will be in her debt.[1] In the last chapter the author writes: "Seven years ago I knew as much about him as the average Australian—that Bass and Flinders sailed the coast of New South Wales when its history began in an heroic little tub, *Tom Thumb*; that Bass discovered Bass Strait, and in a whaleboat; that Flinders made other explorations, creditable but vague. Which was Bass and which Flinders was not quite clear in my mind." Some years ago, when she was sailing in the Gulf of Carpentaria in "a little black lugger", she asked the "doughty skipper", as she saw him swinging the lead for every fathom near Arnhem Land, whether he had no chart. The only chart was one made by Flinders in 1802. Matthew Flinders, as she tells us, became her friend. In her subsequent researches in the libraries of Australia she gathered scraps of information which, when pieced together, made her eyes open in wonder. The story of Matthew Flinders's life as told in this book is true—in no instance has the author played with history. Scenes and situations have been created from written records: dialogue has been founded on fact; and logs, journals, letters and treasured private diaries are the author's authority.

Matthew Flinders made his first journey to the southern seas with Bligh, "the bogy of the Navy", in the ship *Providence*. They visited Van Diemen's Land and Otaheite, returning home by way of Torres Strait and the Dutch settlement at Timor. On his return to England Flinders was drafted to the warship *Bellerophon* (*Billy Ruffin*) and took part in a naval engagement against the French. After this he sailed again to the southern seas with Governor Hunter, and this time Dr. George Bass sailed with him. They sailed on His Majesty's ship *Reliance*, and His Majesty's ship *Supply* sailed with her back to the scene of her former triumph. Bass stowed away in the corner of the longboat, "his first command", His Majesty's Ship *Tom Thumb*, "the infant sister of a wherry, eight feet by five, reeking to high heaven of bad mackerel". *Tom Thumb* was to become famous. Eventually *Reliance* entered Port Jackson. The settlement and what befell Flinders while he was there are described in a chapter "Hell in Heaven"—it was "a dead end of exile, and misery, and starvation". However, Flinders and Bass set out in *Tom Thumb*, with a handy boy, from Sydney Heads. They sailed south, found and named Port Hacking, gave Illawarra its name and discovered black lumps of shale that looked like coal. Back in his cabin on *Reliance* again, Flinders wrote a new name on the map. Before long Flinders had mapped three or four thousand miles of coastline and Bass had discovered Bass Strait—there were two islands instead of one. But the story must be read—it cannot be told here. In the end Flinders came back to England. Before he had sailed away with Hunter he had been betrothed to Ann Chappell. He sought her again, but not before he had been given command of His Majesty's ship *Investigator*, with the rank of captain, that he might survey the unknown parts of New Holland. He married Ann just before he was to sail, to find at the last moment that the rules of the Admiralty forbade her to sail with him. The tremendous decision had to be made and Ann was left behind. We need not follow Flinders in his journey. Ernestine Hill tells the tale in a way that grips the attention. She reveals Flinders as a man of science and of superb determination and fixity of purpose. He put his life's work before everything else, and Ann his wife was no less heroic than he. The tragedy reached its climax when Flinders, after triumphs and trials, was made prisoner at Ile-de-France on his way home. A great part of the book is given over to this stage of his life, and the reader almost lives with Flinders in his cruel exile. In the end he comes home after more than six years in the hands of the French, to find coldness and apathy and lack of appreciation where he expected and surely deserved a warm welcome and realization of his unprecedented achievements. Only Ann is utterly true to him; but life is cruel and the fates give them but four years of poverty and difficulty, and failing health for Flinders. In spite of it all Ann is able in after years to write that during the period they were privileged to live together, not a cloud cast a shadow over the sunshine of their affections, and each day seemed to rivet the attachment more firmly.

Matthew Flinders was a great man. Recognition has come and is still coming to him more than a hundred years after his death. The great majority of Australians are like Ernestine Hill was when she first took Flinders for her friend, as she quaintly puts it. What she has written should be read by Australians young and old and by all who count among the cardinal virtues devotion to duty, sincerity and enduring love. One of the most important facts about this book is to be found in the page devoted to acknowledgements. Here we learn that the Commonwealth Literary Board of the Prime Minister's Department granted the author a Fellowship in 1940, that she might complete the work. This shows an appreciation of values which will be applauded by all who are devoted to Australian history and literature. It was fortunate that such an author as Ernestine Hill was available to hold the Fellowship.

[1] "My Love Must Wait: The Story of Matthew Flinders", by E. Hill; 1941. Sydney: Angus and Robertson Limited. Demy 8vo, pp. 463. Price: 8s. 6d. net.

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REFRACTORY ANÆMIA.

In his study of the bone marrow in anæmia published in this issue, T. E. Wilson has followed the changes occurring in the marrow of several patients after the injection of liver extract and the use of certain other forms of therapy. There is no need to lay emphasis on the value of such a piece of work in the study of the so-called diseases of the blood. While we commend Wilson's study to readers of this journal, that they may gather an idea of what really happens when they use liver therapy in the treatment of anæmia, the time seems opportune for the presentation of an allied subject which has been kept as it were in cold storage for a few weeks. This subject is what is known as refractory anæmia—anæmia in which changes such as those described by Wilson do not occur in the marrow when appropriate treatment with liver, iron and so on is adopted. What is really a monumental piece of work has been carried out by R. R. Bomford and C. P. Rhoads at the Hospital of the Rockefeller Institute for Medical Research, New York City. This work has been published in *The Quarterly Journal of Medicine* for July, 1941; it occupies more than a hundred pages of the journal and should be read carefully by every physician and every clinical pathologist.

Bomford and Rhoads introduce their subject with the statement that the discovery of the therapeutic value of liver and the more general use of efficient methods of administering iron have brought into prominence a group of patients whose course cannot be altered by any known treatment. Some of these patients, they remark, suffer from well-defined entities, such as aplastic anæmia or leucopenic (also known as aleuchæmic) leuchæmia, but others have conditions which do not appear to fall into any recognized category. The disorders dealt with by Bomford and Rhoads are those of patients whose anæmia had failed to yield to any treatment except transfusion of blood. At the same time, cases in which the anæmia was found to be secondary to other diseases, such as cancer, tuberculosis, lymphogranuloma, nephritis, cirrhosis of the liver, sepsis, infective endocarditis and frank leuchæmia, were excluded. Bomford and Rhoads have investigated fifty-eight cases of refractory anæmia, but before any attempt is made to describe their observations, reference must be made to some of their preliminary remarks. They hold that the term "aplastic anæmia" can reasonably be used to include any anæmia in which definite hypoplasia of the hæmopoietic marrow is present. They point out that according to recent accounts the presence in the blood of slight macrocytosis, of immature red and white cells in small numbers, and of an increased percentage of reticulocytes is compatible with the existence of severely hypoplastic marrow at autopsy. They are also clearly correct in the view that the term "aplastic anæmia" cannot be used to describe cases of anæmia, however similar the blood picture may be to that of the accepted condition, if the marrow is not hypoplastic. At this stage, in view of general conclusions to be mentioned later, we do well to remind ourselves that aplasia is regarded as being due either to failure of the cells of the reticulo-endothelial system to produce the differentiated precursors of normal blood cells (from exhaustion, because of the action of some poison or because of the absence of some nutritional or endocrine factor) or to failure of precursor cells to divide in a normal way because of the absence of some maturation factor. In regard to the identification of individual cells in the bone marrow, Bomford and Rhoads find no difficulty with hæmocytoblasts, eosinophile normoblasts, myelocytes and polymorphonuclear leucocytes. One type of cell most frequently found, however, in increased numbers was a medium-sized or small basophile staining cell. After some discussion they express the opinion that this group of cells consists of primary erythroblasts, basophile normoblasts and some atypical erythropoietic cells.

As may be expected with such a condition as refractory anæmia, the classification into types is not simple. Certain types can be described, but they are not sharply defined and some cases appear to be intermediate, between two types. At the same time Bomford and Rhoads believe that the similarity of cases of refractory anæmia as a whole is more significant than the differences between cases and groups of cases. For this reason they think that too much significance should not be attached to a classification into types. The types described by them are four in number. The first is refractory anæmia with partly mature cellular marrow, corresponding, we are told, to the dysplastic phase of anæmia due to hæmotoxic substances; it is the so-called pseudoaplastic anæmia. There were 31 cases in this group. The second type is refractory anæmia with hypocellular marrow, aplastic anæmia or panmyelophthisis. There were 11 cases in this group. The third type is refractory anæmia with immature cellular marrow, chronic granulocytopenia, probably including medullary pseudoleuchæmia. There were 12 cases in this group. The fourth type is refractory anæmia with fibrosis, sclerosis and giant cell hyperplasia of the marrow, or myelosclerosis. There were four cases in this group. The marrow in the first type differed least of all from normal. Though it was immature, some maturation to the stage of normoblast or of polymorphonuclear leucocyte was present and megakaryocytes were usually to be seen. Thus in cases of this type the clinical course was often prolonged, leuco-

penia or thrombocytopenia might be slight or absent, and remissions occurred more frequently than in any other type. In the second group, that of hypocellular marrow or aplastic anæmia, the proportion of fat cells in the marrow to hæmopoietic cells was greatly increased and the number of hæmopoietic cells varied. Thus in two of seven cases in which the marrow was examined, not more than a few groups of two or three small basophile cells were to be found in a whole section of sternal marrow. In several cases there were strands and small groups of hæmopoietic cells, mostly erythropoietic cells, primary erythroblasts, lymphocyte-like cells and relatively few normoblasts, almost all with basophile cytoplasm; occasional myelocytes, almost all eosinophile, and occasional polymorphonuclear leucocytes were seen. No megakaryocytes were seen in any of the marrow from this group. In several cases the distribution was patchy and small areas of actively hæmopoietic marrow were scattered in otherwise distinctly hypocellular marrow. In most cases of the third type, that of refractory anæmia with immature cellular marrow, or chronic granulocytopenia, the marrow was distinctly but not densely hypercellular. It was composed almost entirely of basophile staining cells, with the dark nuclei of normoblasts standing out conspicuously either singly or in groups. Under the high power of the microscope the appearance differed according to the predominating type of cell. In some cases there were numerous hæmocytoblasts and early primary erythroblasts with few late primary erythroblasts and normoblasts. In other cases there were large numbers of smaller cells, some resembling lymphocytes, some resembling plasma cells and some being undoubted primary erythroblasts. Most, if not all, of these cells are regarded as being erythroblasts. The most characteristic features of the fourth type were splenomegaly, anæmia, fibrosis or sclerosis of the marrow and extensive extramedullary hæmopoiesis, the hæmopoietic tissue usually containing conspicuous numbers of megakaryocytes. Bomford and Rhoads point out that the changes in the liver, spleen, lymphatic glands and other organs in the various types differ only in degree. In discussing this statement they remark *inter alia* that degeneration and necrosis of liver cells, probably too severe in many cases to be considered simply as secondary to the anæmia, were present in some cases of the first three types. There is some justification then for the view that refractory anæmia with marrow of the partly cellular type is often a temporary phase in the course of other disorders of the hæmopoietic system. Referring also to the fact, to be mentioned later, that exposure to a single hæmotoxin, benzol, may produce in human bone marrow all the changes described in connexion with refractory anæmia, with the possible exception of basophile sclerosis, Bomford and Rhoads also mention the association between leuchæmia and benzol and add that these observations provide further evidence that the types of refractory anæmia described are closely related conditions and should not be regarded as separate disease entities. The association with leuchæmia need not be further discussed, though it should be pointed out that Bomford and Rhoads state that in their investigations they have encountered a small number of cases which suggested a close relationship between that condition and refractory anæmia.

Thus far the pathological side of the question has been considered with the exception of remissions which will be mentioned later. In the section of their work dealing with the pathology of the condition many case histories are given in full. No attempt can be made to discuss any of these. In Part II of their work, however, Bomford and Rhoads deal with ætiology and treatment; but before these aspects are mentioned it must be stated shortly that refractory anæmia may occur at any age. The oldest patient mentioned in the first part of this monograph was seventy-two years of age and the youngest six months. In some instances a possible association with eunuchoidism, menstruation and the menopause was noted. The incidence of achlorhydria was below the normal incidence. Slight atrophy of the mucous membrane of the edges of the tongue was seen in a few instances, but no disorders of the nails or nervous system were seen in any of these patients. Pigmentation of the skin and occasionally hæmochromatosis occurred as complications of refractory anæmia of the type with partly mature cellular marrow.

This brings us to the question of ætiology. The most obvious fact in this connexion is that no less than thirty-four of the patients were known to have been exposed to a potentially toxic substance, and eleven of these were exposed to benzol. Other substances included hair dyes, volatile insecticides, "Atophan", analgesic drugs and so on. Bomford and Rhoads admit that it is scarcely possible to prove that a certain substance has been the cause of the anæmia, but they insist that from the practical point of view the position is clear. "It is of paramount importance that patients with refractory anæmia should be removed from exposure to any possibly toxic substance, however remote the possibility." They believe that at present no single measure has so great an effect on prognosis. They admit that though severe refractory anæmia may follow exposure to toxic substances, nearly all of which are aromatic hydrocarbons, an apparently identical disorder may occur when there is no evidence of such exposure. This suggests to them that in the latter type of case the disorder might result from the presence of excessive amounts of an endogenous toxic aromatic hydrocarbon, or from failure of the mechanisms which protect the hæmopoietic system from endogenous aromatic hydrocarbons normally present in the body. And it has been shown by Rhoads and Barker in experiments on animals that the body does contain potentially hæmotoxic aromatic hydrocarbons, for anæmia was produced by the use of indol. Rhoads and Barker also showed that that susceptibility of the hæmopoietic system could be conditioned by the administration of a deficient diet, for the postulation of a susceptible state is necessary since the majority of persons are not affected by hæmotoxic substances such as those with which we are here concerned. There is a biochemical mechanism by which normal persons are protected from hæmotoxins. Bomford and Rhoads show that it is theoretically possible that a breakdown of one or more mechanisms of detoxication would render a person susceptible to both endogenous and exogenous aromatic hydrocarbons. It is presumed that the biochemical processes of detoxication take place mainly in the liver and there is evidence of liver damage and of impaired hepatic function in a proportion of cases of refractory anæmia. Bomford and Rhoads, by the use of liver tests, have found the liver function of several of their patients to be defective, and they give good reasons for supposing that the impaired liver function was not the result of the

anæmia. They have also found in this condition a disturbance of pigment metabolism similar to that found in diseases of the liver and in certain forms of exogenous poisoning. Bomford and Rhoads also make brief mention of experiments indicating an abnormality in the lytic substances of the plasma of patients with refractory anæmia. They have investigated saponin lysin in relation to refractory anæmia and also the excretion of glucuronates and sulphates in this condition. As a result of all this they have built up a working hypothesis, which they insist must be "extremely tentative". Their hypothesis of the ætiology of refractory anæmia is:

> . . . that the disorder is due to a conditioned susceptibility to toxic substances, usually exogenous or endogenous aromatic hydrocarbons, associated with hepatic dysfunction, a failure of biochemical mechanisms of detoxication, and the circulation of hæmolytic substances, and that these hæmolysins cause either an abnormal form of hæmolysis and thus an abnormal reaction in the marrow, or that they destroy both circulating red cells and developing cells in the marrow, thus producing hypoplasia or other abnormal forms of marrow.

This hypothesis is interesting and is the logical outcome of some of the observations described. There is an obvious difficulty which arises in regard to the second type of refractory anæmia mentioned. According to the hypothesis, refractory anæmia is a hæmolytic anæmia. If we view aplastic anæmia in the accepted way it is difficult to see how the hypothesis can apply. If, as indeed they may, Bomford and Rhoads apply the term aplastic to any anæmia in which hypoplasia of the bone marrow is present regardless of how the condition of the marrow has been brought about, there would not be so much difficulty. They do remark that it seems unlikely that aplastic anæmia is a distinct entity. The point is of some importance and not purely academic. However, Bomford and Rhoads's hypothesis is only a very tentative hypothesis and does provide an explanation for many manifestations of refractory anæmia. In view of the incomplete state of knowledge on the subject we do well to remember that anæmia is nearly always a symptom of an underlying pathological change. In the present instance the evidence suggests that the pathological change takes place in the liver. In all the circumstances it would be advisable to think not of refractory anæmia as such, but of an anæmia and of a refractory state associated with the anæmia. The occurrence of remissions is in favour of this view, and in any case until the ætiology has been determined such an outlook will make for clarity of thought, if nothing else. The occurrence of remissions would seem to indicate that the cause of refractory anæmia is sometimes intermittent in its action, and we do not know that in its very early stages the anæmia will always be refractory.

Bomford and Rhoads have carried out a valuable and significant piece of work which, as we have already stated, must not be neglected by anyone interested in the blood and diseases that affect it. It will probably stimulate others to investigate this fascinating subject.

A closing observation of another kind must be permitted. This work was carried out in America before America was at war and was sent to England and has been published, in all its length and with all its detail, in an English medical journal while England, at the centre of the Empire, is fighting for its existence. We can imagine no more eloquent tribute to the inherent value of science in a war-racked world.

Current Comment.

INFANTILE BERIBERI.

In some parts of the world beriberi is a very important cause of infantile mortality. The infants are fed at the breast by mothers who are themselves suffering from beriberi and whose milk is therefore deficient in vitamin B_1. The disease becomes manifest usually in the third or fourth month of life. Progress is rapid and death is common. Chronic cases are also observed. Doubtless minor degrees of vitamin B_1 deficiency in infants are almost the rule in communities in which beriberi is prevalent. In severe beriberi, whatever the patient's age, sudden death may occur at any time as a result of acute heart failure; but in infantile beriberi death is to be anticipated unless the appropriate remedy is speedily applied. Our attention has been drawn recently to this disease by a paper by W. R. Aykroyd and B. G. Krishnan.[1] These investigators have conducted a special inquiry into infantile mortality in the Northern Circars district of the Madras Presidency, where beriberi is especially common. Aykroyd, Krishnan, Passmore and Sundararajan have shown that the high prevalence of the disease in this district compared with that in other parts of Madras, and indeed of India as a whole, is due to the different method of milling rice. In the Northern Circars the rice is milled raw, whereas in other places it is first steamed or parboiled to render easier the removal of the pericarp. They showed that, however highly milled, the grain, if parboiled first, retained a quantity of vitamin B_1, whereas grain polished raw retained scarcely any. It is assumed that the process of parboiling causes the vitamin to diffuse through the grain.

The description of infantile beriberi given by Aykroyd and Krishnan is as follows:

> Beriberi usually occurs in breast-fed infants aged 3-4 months. Often the child fails to gain in weight during a week or so previous to the attack. In the acute form the infant is suddenly seized with what appear to be severe paroxysms of pain; during a paroxysm it may straighten out its body and become quite rigid. Between attacks the muscles feel abnormally soft and flabby. Vomiting is frequent. There is usually cyanosis and coldness of the extremities and difficulty in breathing is obvious. Right-sided dilatation of the heart is common and the pulse is weak and rapid. Excretion of urine is diminished. General œdema is rare but localized œdema may be observed. A husky or almost inaudible voice, due to œdema of the larynx and not to paralysis of the vocal cords, is very characteristic of infantile beriberi. The knee-jerks may be absent. Death often occurs within 24 hours unless the appropriate treatment is given.
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> In more chronic cases the usual clinical picture is that of a pale flabby baby, not gaining in weight and becoming weaker and weaker. Vomiting and constipation are frequent. . . .
>
> Examination of the mother will often reveal evidence of beriberi in the form of slight paresis, difficulty in walking and numbness and tingling in the extremities. She will often describe the sudden death of previous infants at the age of 3-4 months or thereabouts.

The diagnosis is readily confirmed by the result of the injection of pure synthetic vitamin B_1. Apparently moribund infants may be revived by this procedure. In less acute cases the administration of yeast extract or rice polishings by mouth might suffice, "witness the success achieved in the Philippines in the treatment of infantile beriberi with 'tiki-tiki', an alcoholic extract of rice polishings". In this regard it is of interest to recall the work of Bray at Nauru, where infantile beriberi became prevalent after the natives had been forbidden to make palm toddy. The Nauruans live on over-prepared modern food, and when toddy was denied them because of its alcohol content they were cut off from almost their sole supply of vitamin B_1. When partially fermented toddy was restored to them the beriberi problem vanished.

[1] *The Indian Journal of Medical Research*, October, 1941.

Aykroyd and Krishnan remark that infantile beriberi has not previously been reported from India, but that, if the experience of other countries is to be taken as a guide, it must be common. They endeavour by statistics to prove that this is so. The infantile mortality rate is higher in the districts in which beriberi is prevalent than in other districts; but what is more significant is the fact that in the beriberi regions 41·8% of the deaths occur among infants aged one to six months, whereas elsewhere only 26·9% of deaths occur in this age group.

Our object in this comment is not so much to discuss the work carried out by Aykroyd and Krishnan as to draw attention to the existence of infantile beriberi. It is well known that varying degrees of deficiency in vitamin B_1 are not uncommon in Australia if classical beriberi is. Furthermore, the artificial feeding of infants with substances deficient in vitamin B_1 is a widespread practice. It is hardly likely that infantile beriberi or something akin to it does not occur in this country. It is worthy of note that the term "convulsions" still appears in vital statistics as an important cause of death in infancy. May it not be that some of these convulsions are manifestations of acute beriberi?

THE KIDNEY IN TRAUMATIC ANURIA.

DURING the last year or two accounts have been published by several authors of a condition known as "crush kidney" or "traumatic anuria". E. G. L. Bywaters and J. H. Dible have investigated the nature of the renal lesion[1] and at the outset they give the following short account of the clinical syndrome:

> In most cases the patient has been buried beneath fallen masonry or heavy debris and on release may appear well except for some swelling of the affected limb. Should shock develop, the blood volume has usually been restored to a normal figure by transfusion and has as a rule been well maintained. Some of these patients pass dark-coloured, smoky or red urine which contains albumin and gives a positive benzidine reaction, and on spectroscopic examination shows the absorption bands of myohæmoglobin . . . The sediment is full of granular debris and brown pigmented casts but only rarely shows red blood corpuscles. Consequently oliguria or anuria may develop, and there is an increase in the concentration of urea, and of phosphate and potassium in the blood. Death may take place about the end of the first week, or recovery may follow a diuresis which occurs about this same time. With either course there is a falling off in the excretion of pigment and of casts, which become more cellular in character.

Bywaters and Dible base their study on material from twenty-two cases of this interesting war-time injury. Their article is illustrated by excellently reproduced photomicrographs, two of which are in colour.

On post-mortem examination the affected muscles appear blanched and show necrotic and reactive changes. The kidneys are large, swollen and rather pale. The capsule strips readily, leaving a smooth surface which may be mottled. On section the cut surface is wet, shiny and œdematous looking and the cortex is swollen and everted. There is sometimes a well-marked zone of pallor in the inner cortical region. Examination of the glomeruli shows that the capsular space is filled with granular eosinophilic débris, which consists either of autolysed epithelial cells or of protein precipitates. In either case the picture indicates glomerular damage possibly associated with an increase in permeability. There are also changes in the lining cells of the capsule, giving the tubular opening a funnel-like appearance. Bywaters and Dible cannot say whether this is the result of metaplasia due to catarrh or whether there is an extension of the tubular epithelium into the capsule. The proximal convoluted tubules are the seat of an intense catarrh, the lumina being filled with detritus and masses similar to those in the capsular space—possibly the remains of necrosed epithelial cells. But it is the ascending limb of Henle and the second convoluted tubule which show the most severe damage. Desquamation, regeneration, necrosis and fibrosis are seen and pigmented casts are present. Where the damage is most pronounced characteristic foci of tubular destruction occur, and in the damaged tubules hyaline casts may be seen, sometimes extending into the surrounding tissue. Later there are signs of commencing disappearance of the affected parts of the nephron together with replacement fibrosis. Myohæmoglobin-pigmented casts are found in the second convoluted tubules and more extensively in the convoluted tubules. These are at a late stage invaded by polymorphonuclear cells.

In discussing this condition, Bywaters and Dible point out first of all that when Minami discussed the renal changes of this syndrome in 1923, he drew particular attention to the blanched muscles and suggested that a search should be made for myohæmoglobin. He thought the condition was an "acute, purely tubular nephrosis". This renal picture is not peculiar to crushing injuries, but may occur in a number of differing conditions. The factor common to many of them is muscle damage. Bywaters and Dible have seen similar histological appearances in a case of tuberculous cachexia and meningitis with gross muscle wasting, in two cases of injury in automobile accidents involving ischæmia of large muscle masses, and in what was apparently a case of idiopathic paralytic myohæmoglobinuria. A practically indistinguishable lesion is also found in the kidneys in excessive intravascular hæmolysis, and in certain cases of blackwater fever similar changes are found in the kidneys. In trying to find an explanation of the condition, Bywaters and Dible point out that anuria in hæmoglobinuria from incompatible blood transfusion has been regarded as due to mechanical blocking of the tubules. This view is taken by J. E. Morison, who has recently investigated the renal tubules in myelomatosis and crush injuries.[1] Morison states that the deposits in myelomatosis appear to be formed slowly, but that they may grow to a large size and show differently stained zones, probably indicating different periods of deposition. He states also that in crush syndrome the casts occur in the same tubular segments, that is, in the distal loops of Henle and in the distal convoluted tubules and collecting tubules. They behave as if they are composed in part of muscle hæmoglobin. They are much smaller than the casts in myelomatosis and thus fewer tubules may appear to be blocked. Tubular epithelial cells show a reaction to the presence of casts, and necrosis may be followed by regeneration. Glomerular changes have not been found by Morison to be significant, and there is no time for the extensive removal of tubules or for increase of fibrous tissue. All the tubules are probably blocked at about the same time, and so there is no opportunity for any one tubule to dilate. Thus a cast blocking a tubule cannot grow by aggregation, as no urine can pass around it. Other observers have postulated in addition to blockage another factor which, they think, produces tubular necrosis of sufficient severity to cause death. Bywaters and Dible give sound reasons for not regarding mechanical blocking as the sole responsible agent. They state quite rightly that if blockage is to produce anuria it must be extensive and must occlude a very large number of nephrons. In twelve kidneys of those in their series casts were found in sufficient numbers in their judgement to make such an explanation possible; in six others, however, the apparent blockage from casts was small, and they find it difficult to believe that in these cases blockage was responsible. Another of their reasons is that the urine was not normal, as it would be if part only of the renal tract was blocked, but was a dilute fluid showing poor concentration of urea and little reabsorption of chlorides. These characters, they hold, are those of a poorly concentrated glomerular filtrate and suggest that the tubules have failed to carry out their function. This finding, in their opinion, agrees with the histological picture of a lesion which is in the main tubular. The diminution in the quantity of the urine, however, indicates that there are other factors in addition to tubular dysfunction and partial tubular blockage. These may be either diminished glomerular filtration due to decreased

[1] *The Journal of Pathology and Bacteriology*, January, 1942.

[1] *Ibidem*, November, 1941.

blood pressure or blood flow, or excessive but unselective reabsorption of the glomerular filtrate through the tubules—in other words, "leakage back into the blood stream". Bywaters and Dible think that the latter of these two possibilities best fits the facts. Their view seems reasonable.

This short account of Bywater and Dible's work should be of interest to clinicians. The condition described by them is traumatic in origin, and an effort should be made to understand it. Clinicians, it is to be hoped, will not have occasion to apply these observations to actual traumatic cases. That the condition can occur apart from trauma is full of interest, and inquiry will naturally turn from this condition to so-called reflex anuria.

VARIX OF THE SPINAL CORD.

VENOUS dilatations and true angiomata of the spinal cord are of interest both from the point of view of the pathologist and of the clinician. To the clinician the chief difficulty lies in diagnosis. J. H. Globus and L. J. Doshay in 1929 discussed the subject fairly fully and reviewed the literature.[1] They referred to the view sometimes expressed that vascular lesions of the spinal cord were rare, and countered this by presenting records of 28 verified cases from the literature and by adding that the list did not exhaust all the reported cases. They divided the lesions into three groups: a group of venous dilatations; a group comprising arterial or arterio-venous aneurysms; hæmangiomata, consisting of intramedullary, extramedullary, extradural and vertebral types. They stated that the largest group was the first, that of venous dilatations. Many names had been applied to these dilatations, such as pial hæmorrhoids, circoid aneurysms of the spinal veins, varicose dilatations of the spinal vains, *angioma venosum racemosum* and angiomata. They grouped all these under the single term dilatations of the spinal veins. Globus and Doshay discussed the views of several authors regarding causation. Kadyi described two types of varices, both of which he attributed to mechanical factors. Benda quoted Rokitansky, who also laid stress on the mechanical hindrance to the blood flow as the all-important factor. He recognized, however, that purely mechanical factors did not explain all the phenomena observed in venous dilatations—some concomitant or preexisting alteration in the involved veins is considered an additional factor. Degenerative, sclerotic or inflammatory changes are regarded by many as being probable predisposing conditions. Benda, we are told, dismissed as unwarranted by the known facts any suggestion that there might be a congenital weakness in the vessel. It is quite refreshing to find this suggestion not dragged in to explain our ignorance in such a case! Globus and Doshay point out that the older views of Kadyi and views such as Rokitansky's agree that by impairing normal return of venous blood abnormal postures have an important bearing on venous dilatations.

An interesting example of varix of the spinal cord has recently been reported by G. A. Ransome and E. C. Mekie.[2] The patient was an intelligent Chinese clerk, aged thirty-two years, who gave a clinical history extending over eight years. After a preliminary attack of pain in the legs he had an interval of four years without symptoms. Then followed gradually increasing weakness in the legs, disturbance of sensation, disturbance of micturition, impotence and finally a spastic gait. At no time in four years was there any pain suggestive of a root origin. Ransome and Mekie describe the clinical findings in full and reproduce a chart showing the cutaneous areas of hypoalgesia and anæsthesia. The most interesting feature of the clinical examination was the findings on X-ray examination. Lipiodol was injected by cisternal puncture, and the X-ray picture revealed a partial block at the lower border of the fifth cervical vertebra. On fluoroscopy the lipiodol was seen to run down in five or six tortuous little tunnels, "not unlike barium running through a malignant growth of the œsophagus". Exploratory laminectomy was performed, but when the varix was exposed on incision of the dura, respiration became irregular, pulse rate rose and blood pressure fell. Nothing could be done to the varix and the patient died half an hour later. Post-mortem examination of the specimen showed that the tumour was two centimetres long and measured one and a half centimetres from side to side. Histological examination showed that the tumour was a varix of the spinal *pia mater*. Ransome and Mekie point out that there are three clinical features which may be helpful in the diagnosis of this condition. They are: (i) A previous history of a spinal episode, which may range from a "lumbago" to a painful "diplegia", usually with some or complete recovery. (ii) A fluctuation of symptoms daily or over a period of time. (iii) The presence of angiomata elsewhere in the body, especially if they are in the same segment as the suspected lesion. After lumbar puncture Ransome and Mekie's patient had pain, and this has been the experience of other authors. The radiological appearances should be borne in mind, for they should make diagnosis possible.

[1] *Surgery, Gynecology and Obstetrics*, Volume XLVIII, 1929, page 345.
[2] *The British Journal of Surgery*, January, 1942.

INTRAVENOUS ADMINISTRATION OF OXYGEN.

THE possibility of relieving anoxæmia by intravenous administration of oxygen has been recognized for some considerable time, and many experiments on animals have been conducted and not a few attempts made on the human subject. In 1902 F. Mariani injected 120 cubic centimetres of oxygen in forty-five minutes into a vein of a moribund tuberculous patient and noted some temporary improvement.[1] F. W. Tunnicliffe and G. F. Stebbing in 1916 reported two cases of cyanosis relieved by intravenously administered oxygen and recommended this as a therapeutic measure.[2] The latest advocate of this procedure is Edwin E. Ziegler, of Boston, who holds the view that failures of others in the past were due to faulty technique, in that generally far too much of the gas was given.[3] Ziegler ignores research carried out in Australia, but comments on the investigation carried out by Geoffrey Bourne and his collaborator R. G. Smith.[4] The conclusions set out by these authors are not welcome to Dr. Ziegler: "It is seen, however, that in amounts that would provide some hope of the supply of an adequate amount, pulmonary embolism and right heart insufficiency produce an even greater degree of anoxæmia than that already in existence."

Ziegler describes an apparatus not very different from others employed in physiological laboratories for the same purpose. The therapeutic amounts of oxygen for intravenous use are, according to him, 200 to 600 cubic centimetres per hour, and the larger quantity, he points out, is much less than the total requirement, and therein he sees the success of his technique.

There are two important criticisms to be levelled against Ziegler's recommendations. Despite his assurance, there is always a possibility of the occurrence of nitrogen embolism in the lungs even if a 99·8% oxygen is used. The late J. S. Haldane suggested that a bubble of oxygen in the lung would behave like the bubble in Krogh's aerotonometer and quickly equilibrate with the alveolar air, four-fifths of which are nitrogen. The second indictment of Ziegler's contention is that whilst the entry of oxygen is provided for, the escape of carbon dioxide is ignored. A brief consideration of the matter will bring one to the conclusion that the added oxygen will increase the production of carbon dioxide though it may lessen the formation of lactic acid. Ziegler actually states that oxygen given intravenously in the amounts he recommends produces "slowing of the pulse rate and a less laboured and slower respiration", precisely the conditions to aggravate the carbon dioxide narcosis.

[1] *Riforma medica*, Volume XVIII, 1902, page 194 (quoted by Ziegler).
[2] *The Lancet*, Volume I, 1940, page 992.
[3] *The Journal of Laboratory and Clinical Medicine*, November, 1941.
[4] *American Journal of Physiology*, Volume LXXXII, 1927, page 328.

Abstracts from Medical Literature.

PÆDIATRICS.

Sulphapyridine Dosage in Childhood Pneumonia.

SAMUEL I. ELLENBERG AND HARRY S. ALTMAN (*Archives of Pediatrics*, October, 1941) point out that although chemotherapy has now been established as an advance in the treatment of pneumonia, the problems of optimum dosage, proper intervals of administration, and the most effective method of administration of these drugs without the production of toxic reactions still require solution. The author's study in this direction indicates that for children above the age of two, when the prognosis, particularly in lobar pneumonia, is known to be very good, a lower sulphapyridine dosage schedule will have the desired effect of ensuring a good prognosis, a prompt subsidence in the temperature and in the toxicity of the pneumonia process, and in addition will be accompanied by a lower incidence of toxic manifestations from the drug than was obtained with the higher dosage schedule. In the lower dosage schedule 0·1 gramme per kilogram of body weight is given for the first twenty-four hours, equal doses being given at intervals of four hours. On the next day this dose is given at intervals of six hours, and on the following day the same dose is given three times a day until one day of normal temperature is obtained, after which the drug is stopped. Under the age of two, however, it would appear best to use the higher dosage schedule of sulphapyridine. In this schedule 0·2 gramme per kilogram of body weight is given for the first twenty-four hours, divided into six equal doses and given at four-hour intervals. The next day the dose is 0·1 gramme per kilogram of body weight, and it is given in divided equal doses at four-hour intervals. This last dose is then continued three times daily on the third day and thereafter until a normal temperature is obtained for three days. The authors found that the higher dosage was particularly useful in bronchopneumonia, and especially when the streptococcus was the responsible organism, since the prognosis is far more serious in this age group and the response at best to sulphapyridine is less favourable. Further, irrespective of the dosage, the incidence of empyema has been decreased as compared with the incidence in previous years. It was also observed that of the empyema patients who had received sulphapyridine, a smaller number required surgical intervention, because the chest fluid was thinner and could be successfully removed by aspiration. Fewer toxic manifestations of sulphapyridine were observed in infants and young children as compared with the older children.

Cardiac Signs in Rheumatic Infection Of Childhood.

RACHEL ASH (*American Journal of Diseases of Children*, January, 1942) has made an analysis of the cardiac signs for a group of some five hundred children with rheumatic infection who had been followed for an average period of nine and six-tenths years from the onset of the illness. The presence of clinically demonstrable heart disease is of less importance as a guide to the management of a child with rheumatic infection than evidence indicating the existence of active infection. Such infection may be present when the heart seems normal. Information of value in determining whether the inflammatory process is progressing or regressing may, however, often be secured by careful consecutive examination of the heart. Thirty-eight *per centum* of the children presented no definite clinical evidence of cardiac damage as a result of the initial illness. It is probable that pathological examination would have disclosed changes in the hearts of many of them indicative of rheumatic infection, possibly of minimal degree. In 19% of this group, for whom a diagnosis of valvulitis was not made at onset, definite valvular damage subsequently developed; in 80%, however, this damage was the result of an acute recrudescence of the disease. The valvular damage which developed in six of the children in the seeming absence of infection and after a prolonged latent period may be interpreted as due to continued subclinical activity of the infection or to progresive fibrosis in the healing stage of infection of a valve which had failed to disclose its initial damage by clinical signs. The vastly higher death rate for the children with obvious carditis at onset was to be expected and can be attributed to the severity of the myocardial involvement. The fact that the death rate for children with seemingly normal hearts at onset tended to be relatively low during subsequent recurrences indicates that such children were suffering from a milder form of rheumatic infection or had possessed or had attained greater immunity and decreased myocardial susceptibility. Disappearance of physical signs of heart disease occurred in 10% of the children who had presented signs of cardiac damage after recovery from the initial infection. Minimal anatomical changes probably persist in many of these patients. If one bears in mind the insidious appearance of mitral stenosis in a few children who had shown no initial evidence of heart disease, it is to be expected that some patients in this group in which regression of cardiac signs has occurred will in future show evidence of mitral stenosis. The apical systolic blow which occurs early in rheumatic infection in association with some degree of cardiac enlargement is due to incompetence of the mitral ring. However, at such a stage of the infection autopsy practically never fails to reveal inflammatory changes in the leaflets of the mitral valve which are definite, even though non-deforming. Since the valvular ring at this time is dilated rather than stenosed, the presence of an apical mid-diastolic murmur is not an indication of anatomic stenosis, but rather a manifestation of active infection. Such a mid-diastolic murmur may disappear with subsidence of the infection. The shortest interval before the appearance of the rumble of mitral stenosis in the present series was two years and the average interval was five years from onset. In approximately half of the cases no mid-diastolic blow preceded the appearance of the stenotic rumble. A clue to the existence of active carditis is the presence of a peculiar high-pitched whistling screech, likened by some to the call of a seagull. It is usually heard in the region of the apex as a component of the mitral systolic blow, but may occasionally be audible over the entire precordial region. Still expressed the opinion that the supervention of a musical character to the bruit of rheumatic endocarditis is a sinister omen which generally points to severe progressive endocarditis. The murmurs of both mitral stenosis and aortic insufficiency tended to be inconstant at onset. The appearance of the peripheral signs of aortic insufficiency as a rule was delayed for months or years after the appearance of the murmur. Aortic stenosis was rare and supervened only after years of insufficiency. Acute pericarditis had the most ominous prognosis followed in order of severity by aortic insufficiency and combined mitral stenosis and insufficiency.

Mercury Poisoning from Topical Application of Fifteen Per Centum Ammoniated Mercury.

CHARLES L. WILBAR (*The Journal of Pediatrics*, January, 1942) reports a case of mercury poisoning in a child eighteen months old caused by the daily application of an ointment of 15% ammoniated mercury to skin areas for three weeks, followed by use of the same ointment diluted in equal portions with lard for a period of ten days. A concentration of four milligrammes of mercury per litre was found in the urine. The poisoning affected mainly the skin, causing a generalized exfoliative dermatitis. There were also some stomatitis and moderate œdema and cyanosis of the hands and feet. There appeared to be no renal damage in the case reported.

Blood Sedimentation Rate in Acute Glomerulonephritis.

MITCHELL I. RUBIN, MILTON RAPOPORT AND ARTHUR D. WALTZ (*The Journal of Pediatrics*, January, 1942) have followed the course of acute glomerulonephritis by means of the blood sedimentation rate in a group of forty patients admitted to the wards of the Children's Hospital of Philadelphia. Simultaneously Addis counts were made and blood sedimentation rates estimated at two-week intervals. Routine examinations of urine were made more frequently and periodical assessment of renal function by the urea clearance test and phenolsulphonephthalein excretion test was carried out. The various criteria commonly employed in assessing complete recovery from an attack of acute nephritis are not entirely satisfactory. The most commonly used and simplest of the many tests, the routine examination of urine, obviously is no criterion of complete healing of the renal lesion, since the Addis sediment count reveals abnormalities long after careful routine urinary examination fails to reveal abnormalities. Certainly a "normal" renal function, estimated by any of the commonly employed renal function tests, does not preclude a continued activity of the disease, for often in early stages, when hæmaturia is still grossly present, the phenolsulphonephthalein excretion test or urea clearance test may give entirely normal results and continue to do so in face of persistent and prolonged hæmaturia. The sediment count of Addis is the most sensitive indication of the continued activity of the disease. However, because of the technical difficulties involved, this test has not attained the widespread usage which it deserves. Certainly in out-patient and home practice with children the added

possible inaccuracies of performance of the test makes its use more difficult. As a result of their investigation the authors consider that there is a close correlation between the return of the sedimentation rate to normal and recovery from acute glomerulonephritis. There is a correlation between the return of the sedimentation rate and the Addis count, the Addis count becoming normal about five weeks after the sedimentation rate. In those instances in which there has been great disparity between the return of the sedimentation rate and the Addis count to normal the sedimentation rate has been an equally if not a more reliable prognostic index than has the Addis count. However, of even greater prognostic significance is the return of both the Addis count and sedimentation rate to persistently normal levels for a period of several weeks. Finally, the simplicity of the sedimentation rate test, which seems to be a valuable guide of the course of acute glomerulonephritis, recommends its use in this disease.

ORTHOPÆDIC SURGERY.

Fresh Compound Fractures Treated by Sulphonamides and in Selected Cases by Internal Fixation.

WILLIS C. CAMPBELL AND HUGH SMITH (*The Journal of the American Medical Association*, August 30, 1941) present a comparative analysis of treatments applied to 218 fresh compound fractures. One hundred and forty-three patients were treated with sulphonamides, and internal fixation was used in 42 of these cases; 75 were treated without internal fixation and without administration of sulphonamides. The fractures were classified under three headings: mild, moderate and severe; *débridement* was carried out in all cases. In the mild group *débridement* was limited to the superficial tissues. Pistol shot fractures were treated as closed fractures except when an important nerve, tendon or vessel had been severed. In moderate and severe fractures meticulous cleansing was practised, followed by irrigation of the wound with saline solution; complete hæmostasis was secured. In the 42 fractures treated by internal fixation, vitallium was principally used, this metal being tolerated by the tissues to a much greater degree than the highly electrolytic alloys formerly used. Five to twenty grammes of sulphanilamide crystals were placed in the wound and carefully distributed throughout. In deep wounds a few interrupted catgut sutures were used. The skin was loosely approximated with silk. In a few cases only was "Vaseline" gauze packing used. Sulphathiazole was given by mouth post-operatively as soon as nausea ceased, in doses of one gramme every four hours. The end results in the two groups are given. There was approximately the same percentage of union and non-union, and the average time required for union was approximately identical. Primary wound closure, in conjunction with sulphonamide therapy, did not increase the incidence of gas gangrene, nor was there sufficient decrease to indicate any special beneficial effect of the drug against gas-forming organisms. The incidence of infection was reduced from 33·3% to 18·1%. The authors' conclusion is that the use of sulphonamides, in conjunction with meticulous wound toilet, has broadened the applicability of internal fixation and primary closure with improvement in end results.

Bone and Cartilage Transplants.

RAINSFORD MOWLEM (*The British Journal of Surgery*, October, 1941) discusses the use and behaviour of cartilage and bone transplants. His findings are based on (*a*) 40 cases of cartilage transplant and (*b*) 115 cases of iliac bone transplant. The cartilage grafts were made chiefly in the nose and to reconstruct the ear. He discusses the operative technique in the first group, in which the grafts were divided into two types, autografts and homografts; with regard to the second type he refers to the use of cadaveric cartilage stored in merthiolate solution, and states that the method has some popularity in America. There is no clinical difference between autografts and homografts. The right seventh costal cartilage is the usual donor area. Whenever cartilage is used there is little evidence of tissue reaction. Cartilage is relatively avascular and does not undergo absorption; microscopic examination reveals that the cellular structure of the transplant is relatively normal. The reaction of the transplant to infection is poor, and even early drainage seldom saves it. Occasionally costal cartilage is encountered which is so spongy as to be almost valueless as a support. A certain proportion of transplants, which seem perfectly satisfactory when inserted, become distorted within a few months; attempts to control the tendency to distortion of cartilage grafts have been unsuccessful. The use of cartilage was so unsatisfactory that the author abandoned it about seven years before the paper was written. With regard to the bone grafts, the author states that the grafts were used in the following ways: (i) to restore the nasal bridge, (ii) to restore lost continuity of the jaw (interstitial mandibular grafts), (iii) in the mandibular or maxillary regions to restore contour (superimposed grafts), (iv) to reconstruct frontal bone defect. In 102 of the 115 cases under consideration the transplant was made to the nasal bridge; in 66 of these cases bony union with the underlying bones has been obtained. There appears to be no clinical or radiographic difference between adherent and free grafts. The immediate local reaction of the recipient area seems to be a little greater than in the case of cartilage; possibly this is due to additional trauma. From the clinical viewpoint, only slight alteration occurs in the appearance of the transplant, except that irregularities tend to become rounded off during the first two or three months. After the initial period of slight alteration the graft persists in an unchanged state, with the exception of transplants made before ossification of the epiphysis of the iliac crest; in these cases the total bulk of the graft continues to diminish for as much as six months, by which time perhaps one-half of it has been absorbed. Reaction to infection is surprisingly good. The author describes in detail X-ray and histological findings of bone grafts, and briefly reviews the literature of the subject. He concludes that there is evidence to show that bone grafts survive transplantation and that the survival is dependent neither upon union of the graft with growing bone nor upon the presence of periosteum; rather does this survival depend upon the fact that the bone structure is such that early permeation by tissue fluids enables the bone cells themselves to survive. The use of dense transplants, such as tibia, which may be satisfactory for purely orthopædic purposes, may not result in the survival of the transplant itself, owing to the mechanical form of the bone, which prevents the early establishment of cell nutrition. The conflicting opinions expressed in the literature may be due entirely to the use of different textures of bone as the basis for experiment.

Spontaneous Fracture of the Neck of the Femur.

KENNETH S. MULLARD (*The British Journal of Surgery*, October, 1941) reports a case of spontaneous fracture of the neck of the femur in the absence of any observable bone disease; he states that it is the first such case reported in the English literature, and he gives a brief review of the relevant literature from other countries. The patient, a soldier, aged twenty-seven years, was a member of a unit that underwent the most intensive training in the British Army. Four months after joining the unit he went for a cross-country run of four miles, as he had often done before, and afterwards noted stiffness in the left hip. Three days later he went for a route march, but had to "fall out" after nine miles on account of increasing pain in the left hip. He undertook no further exertion until the unit returned to billets nine days later, when he was sent to hospital, barely able to hobble along. A skiagram revealed a transcervical fracture of the neck of the left femur, half an inch proximal to the intertrochanteric line and parallel to it. The fracture showed as a gap in the continuity of the upper margin of the neck, passing into the bone at a right angle to the cortex; thence it was continued across the neck as a fine, irregular but nevertheless definite line, terminating with splintering of the cortex of the lower margin of the neck. The fracture appeared to be an abduction fracture, with a gap at the upper and outer margin of the neck and splintering and impaction at the lower and inner margin. The right hip was normal and the fracture did not show in the lateral view. The patient's symptoms rapidly disappeared after a few days in bed with non-weight-bearing movements, and suitably graduated weight bearing was later introduced; seven weeks after his admission to hospital repair was almost complete. The young man was perfectly healthy, and no evidence of bone disease was found. The serum phosphorus content was 3·6 milligrammes *per centum* by King's method (normal), and the serum calcium content was 9·2 milligrammes *per centum* by Trevan and Bainbridge's method (lower limit of normal). The author states that the points of interest are: (i) the absence of any history of injury, even after close and repeated questioning; (ii) the history of repeated severe physical strain; (iii) the gradually increasing disability, rapidly relieved by rest; (iv) the normal appearance of the bone texture as seen in the skiagrams; and (v) the gradual obliteration of the fracture line without the appearance of callus. The similarity of this case to other cases of march fracture is discussed, and the author points out that such fractures are likely to increase in frequency during the war.

Naval, Military and Air Force.

THE DANGER OF ACUTE PERNICIOUS MALARIA IN TROOPS AND REFUGEES FROM THE SOUTH-WESTERN PACIFIC ZONE.

THE following note on the danger of the occurrence of acute pernicious malaria among troops and refugees from the South-Western Pacific zone is published at the request of the Director-General of Medical Services.

Refugees and troops, many of whom have recently spent much time in tropical jungles and swampy country in the South-Western Pacific zone, are arriving in Australia. They have been subjected to the risk of tropical diseases which may be latent and unsuspected at the time of their arrival and which may only become manifest clinically many weeks, months or even years later. Apart from the danger that they may act as carriers and introduce parasitic diseases into Northern Australia, they constitute a risk to themselves until such infection be diagnosed and treated.

Civilian practitioners may be called in to treat such troops when on leave or after their discharge from the army. Under such circumstances it is important to remember the possibility of such parasitic diseases as malaria, intestinal or hepatic amœbiasis, ankylostomiasis and the like. Some may give a frank history of malaria fever. Others—especially those who have been receiving suppressive treatment with quinine (so-called quinine prophylaxis)—may never have manifested primary fever.

Within a period of three weeks after the daily dose of five grains of quinine has been discontinued, many latent cases develop clinical malaria. This may take the form of:

1. Classical quotidian, tertian or quartan fever or
2. Acute pernicious malaria manifesting itself by hyperpyrexia or signs of involvement of the nervous system including coma, profound cardio-vascular shock, severe vomiting, diarrhœa, hæmatemesis, anæmia, jaundice, etc.

The commonest fatal cases belong to the cerebral, algid and cardio-vascular types.

In cerebral malaria the coma may come on rapidly or the patient may more gradually pass from a condition of apathy and drowsiness to one of stupor and coma. In other instances there is great excitability with a tendency to violence; delirium and convulsions may precede the onset of coma. The face is suffused, the pupils contracted and the reflexes often modified. The temperature is usually high and various pareses may develop. The spleen may not be palpable and parasites (*Plasmodium falciparum*) are sometimes scanty in the peripheral blood.

In algid and cardiac malaria the patient presents a picture of cardio-vascular shock. There is a Hippocratic facies, the skin is cold and covered with clammy sweat. The respirations are shallow, the pulse is rapid, thready and weak, and the blood pressure very low. Vomiting, diarrhœa, epigastric and lumbar pain may occur. Though the skin temperature is often low the rectal temperature is usually high. Parasites (*Plasmodium falciparum*) are as a rule found easily in peripheral blood smears, but this may not be so if the patient has been having suppressive quinine treatment. In any case thick as well as thin blood films should always be examined by a competent pathologist in patients suspected of suffering from acute pernicious malaria.

Patients with acute pernicious manifestations are gravely ill. They should receive an intravenous injection of quinine bihydrochloride (grains x) in 0·85% saline solution immediately, and this can be repeated when necessary within six hours. Delay means death. These injections should be given slowly so as to avoid an unnecessary fall of blood pressure, and the volume of fluid administered may vary from 10 cubic centimetres to one pint. The concentration of quinine used, however, should not exceed one grain to one cubic centimetre.

Quinine bihydrochloride (grains x in 10 cubic centimetres of 0·85% saline) may be injected intramuscularly where the intravenous route cannot be employed. When the patient can swallow and vomiting has ceased, 10 grains of the bisulphate of quinine or some other suitable salt should be given orally thrice daily for three days. This is followed by a course of "Mepacrine" ("Atebrin"), 0·1 gramme thrice daily after food for five days, and after a two days' interval by a course of "Pamaquin" ("Plasmoquine"), 0·01 gramme thrice daily after food for another five days. If the new synthetic drugs are not available, 10 grains of quinine bisulphate or other suitable salt should be continued thrice daily for seven to ten days, and then twice daily for a similar period.

MEDICAL ATTENDANCE ON MEMBERS OF THE ROYAL AUSTRALIAN AIR FORCE ABSENT FROM THEIR UNITS.

THE following notes relating to the medical attendance on members of the Royal Australian Air Force who are absent from their units are published for the information and guidance of medical practitioners at the request of Air Commodore Victor Hurley, Director of Medical Services of the Royal Australian Air Force.

Area medical officers will not be allotted to members of the R.A.A.F.

Instructions have been issued that a member, on becoming ill or sustaining injury while on leave, is to communicate promptly with his unit.

If instructed to do so, he may call in or attend a local doctor.

In a case of emergency or in a remote locality, he may seek medical attendance prior to communicating with his unit.

He is to produce as evidence of his bona fides his leave pass, identity disk or paybook.

A fee of 7s. 6d. per visit is payable for such attendances as, in the circumstances, are considered reasonable.

A certificate, preferably on R.A.A.F. Form P/M 1 or Army Form A.46, showing number, rank, name, initials, unit, date, nature of disability and estimated period of unfitness is to be supplied to each member for immediate transmission to his unit.

As only a member's own unit is in a position to certify to his illness, absence, etc., duplicates of certificates should be sent from time to time to each unit concerned, accompanied by a claim for attendances upon the members of that unit shown on the certificates attached.

Certificates and claims sent elsewhere cannot be dealt with and may be returned for correct disposal.

Prescriptions written for duration personnel under the above scheme should be limited to the regulation scale and should be endorsed with the full official particulars (including unit) of the members concerned.

Chemists are being circularized with reference to dispensing for these personnel.

General.

Arrangements for admission to appropriate hospitals should be made through member's unit medical officers whenever possible. In any case, number, rank, name, initials, unit address and diagnosis should always be advised.

It would be greatly appreciated if area medical officers would pay particular attention to the following points:

(*a*) Sick leave should be limited to an absolute minimum, consistent with the proper treatment of the patient. (This is necessary as so many of our personnel are undergoing courses of technical training and even a short period of sick leave interferes seriously with this training.)

(*b*) In a case where treatment is likely to be prolonged, arrangements should be made with the member's unit medical officer for his admission to a R.A.A.F. hospital or station sick quarters. The service is now in a position in most cases to provide any medical, surgical or investigational treatment required, and in future it will not be necessary to make use of Repatriation hospitals to any great extent.

(*c*) The utmost care should be exercised in issuing a certificate where a member reports to an area medical officer some days after the alleged onset of his disability or seeks a retrospective certificate to cover the whole period of his disability. It is realized that in this respect area medical officers are rarely at fault and that where this has been done it is usually by a civilian practitioner, unappreciative of service requirements. The matter is mentioned here only because it is of the utmost importance to guard against abuse of the privileges of medical attendance.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 115, of April 16, 1942.

PERMANENT NAVAL FORCES OF THE COMMONWEALTH (SEA-GOING FORCES).

Fixing Rates of Pay.—Surgeon Lieutenant Frank Frederick Coffey is paid the rates of pay and allowances prescribed in the Naval Financial Regulations for Surgeon Lieutenant-Commander (on promotion), whilst acting in that rank, dated 12th February, 1942.

AUSTRALIAN IMPERIAL FORCE.

Australian Army Medical Corps.

The undermentioned officer is appointed from the Reserve of Officers to a unit of the Australian Imperial Force as from the date and in the rank indicated:

To be Captain.—Honorary Captain A. E. McGuinness, 13th December, 1941.

The undermentioned are appointed to the Australian Imperial Force as from the dates and in the ranks indicated:

To be Captains and are seconded.—Louis Vivian Church and Geoffrey Patrick Dynon, 10th February, 1942, William Lister Sloss, 13th February, 1942, and James Adrian Paul, 14th February, 1942.

The following change is made:

Captain C. C. Wark is transferred from Reinforcements, with regimental seniority in accordance with his Army seniority, 1st February, 1942.

AUSTRALIAN MILITARY FORCES.

Australian Army Medical Corps.

Lieutenant-Colonels (Temporary Colonels) C. L. Chapman, D.S.O., V.D., and A. M. McIntosh are appointed Deputy Directors of a Service and retain the temporary ranks of Colonel, 5th January, 1942.

Captain (Honorary Lieutenant-Colonel) V. McDowall from the Reserve of Officers is appointed to command a General Hospital and to be Lieutenant-Colonel (temporarily), 1st January, 1942.

Major D. R. Brown, M.C., and Captain (Temporary Major) K. A. McGarrity are appointed to command Field Ambulances, 8th October, 1941, and to be Lieutenant-Colonels (temporarily), 23rd February, 1942.

Captain (provisionally) B. T. Mayes is transferred to the Reserve of Officers (A.A.M.C.), 30th May, 1941.

The notifications respecting the appointments of Captains (provisionally) D. G. Duffy and J. Watson which appeared in Executive Minutes Nos. 170/1940 and 198/1940 respectively, promulgated in *Commonwealth Gazettes*, Nos. 181 of 1940 and 213 of 1940, respectively, are withdrawn.

The following officers are appointed from the Reserve of Officers (A.A.M.C.) and to be Captains (provisionally) and where transferred are transferred with regimental seniority in accordance with Army seniority: Honorary Captains W. E. King, 4th November, 1940, and is transferred, 24th March, 1941, and to be Major (temporarily), 27th January, 1942, W. G. Heaslip, 23rd June, 1941, and is transferred, 2nd March, 1942, D. M. Crooks and E. L. Abrahams, 1st February, 1942, K. Brennan, and is seconded, 25th February, 1942, C. W. England, 6th March, 1942, and N. C. Lee Tet, 16th March, 1942.

Captain A. J. May is appointed from the Reserve of Officers (A.A.M.C.), 17th February, 1942.

To be Lieutenant-Colonel (temporarily).—Captain (Temporary Major) N60115 E. S. A. Meyers, 16th February, 1942.

To be Majors (temporarily).—Captains H. A. Retallick, 9th January, 1942, N8405 M. M. Kennedy, 6th March, 1942, and V29342 I. Buzzard, 7th March, 1942.

To be Captains (provisionally).—Frank Dudley Smith, 7th March, 1942, Thomas Natal Bolger, 10th March, 1942, Albert James Reye, 11th March, 1942, Alexander Hayward Parker and Henry Earle Goodman, 14th March, 1942.

Captain (Temporary Major) J. W. Ralston is appointed to command a Light Field Ambulance, 11th January, 1942, and to be Lieutenant-Colonel (temporarily), 13th February, 1942.

Captain (Temporary Major) N58614 R. V. Bretherton is appointed to command a Field Ambulance, 18th January, 1942, and to be Lieutenant-Colonel (temporarily), 1st March, 1942.

Lieutenant-Colonel N278611 J. R. M. Beith, D.S.O., is transferred from Australian Army Medical Service, Australian Imperial Force, and is appointed to command a Convalescent Depot, 10th February, 1942.

Lieutenant-Colonel (Honorary Colonel) W. L. Kirkwood, O.B.E., V.D., from the Reserve of Officers, is appointed to command a General Hospital, 12th December, 1941.

Lieutenant-Colonel T. G. Ross, D.S.O., from the Retired List, is appointed to command a General Hospital, 12th December, 1941.

Lieutenant-Colonel E. S. Meyers, V.D., from the Reserve of Officers is appointed to command a General Hospital and to be Colonel (temporarily), 20th February, 1942.

Captains (provisionally) S1434 C. Chambers and S34263 W. F. Joynt are transferred to a Regimental Supernumerary List, 2nd March, 1942.

The following officers are appointed from the Reserve of Officers (A.A.M.C.): Lieutenant-Colonel T. M. Furber, 19th February, 1942, Captains Q119626 H. Crawford, 20th October, 1941, and to be Major (temporarily), 27th February, 1942 (in lieu of the notifications respecting this officer which appeared in Executive Minutes Nos. 212/1941 and 227/1941, respectively, promulgated in *Commonwealth Gazettes*, Nos. 247 of 1941 and 266 of 1941, respectively, and D. H. Bodycomb, M.C., 25th February, 1942.

The following officers are appointed from the Reserve of Officers and to be Captains (provisionally): Honorary Captains D. Klineberg, 13th January, 1942, N278622 C. J. Zimmerman, N278621 L. T. Shea, 30th January, 1942, and K. F. O'Donnell, 25th February, 1942.

To be Lieutenant-Colonel (temporarily).—Captain (provisionally) (Temporary Major) P. W. Hopkins, M.C., 12th February, 1942.

To be Captains (provisionally).—Geoffrey Hampden Vernon, 25th February, 1942, Eric Campbell Wilson, 17th March, 1942, Allen John Christophers, Thomas Edward Wilson and Barbara Joyce Burfitt, 20th March, 1942.

The name "E. J. Swan", which appeared in Executive Minute No. 40/1942, promulgated in *Commonwealth Gazette*, No. 63 of 1942, is amended to read "E. J. Swann".

To be Honorary Captains.—Anton Emil Diethelm, 16th February, 1942; Richard Row, 12th March, 1942; and Alan Mostyn Bradford Grant, 16th March, 1942.

ROYAL AUSTRALIAN AIR FORCE.

Citizen Air Force: Medical Branch.

The following are appointed to commissions on probation with the rank of Flight Lieutenant with effect from the dates indicated: Leaton Elias, M.B., B.S. (3736), William Arnold Hillman, M.B., B.S. (3735), 16th February, 1942; Donald Fergus Buckle, M.B., B.S., D.P.M. (3865), 23rd February, 1942; Hugh Carlyle Taylor, M.B., Ch.M. (4368), 26th February, 1942; Ronald Justine Carlisle Kristenson, M.B., Ch.M. (4418).

The following are appointed to commissions on probation for part-time duties with the rank of Flight Lieutenant, and are promoted to Temporary Squadron Leader with effect from the dates indicated: Basil William Birkenhead Riley, M.B., Ch.M., F.R.C.S. (4370), 26th February, 1942; William Thomas Daly Maxwell, M.B., Ch.M., F.R.A.C.S. (4363), 27th February, 1942.

The probationary appointments of the following temporary Squadron Leaders are confirmed: G. Finlay (2617), W. A. Harms (2757).

The probationary appointments of the following temporary Flight Lieutenants are confirmed: S. K. Wilson (1227), R. M. Kavanaugh (1881), N. T. Wood (1882), R. W. Foley (1898), H. T. Harvey (1924), T. G. Thorpe (2074), A. T. Williams (2096), R. F. Porter (2115), D. McK. Ross (2292), J. C. Homewood (2304), A. L. Cohen (2374), (Acting Squadron Leader) J. S. Baird (1481), S. Bremner (2568), A. C. Dalziell (2754), D. J. Dooley (2834), G. V. Gengos (2861), T. E. Henderson (2862), J. T. Brook (2863), J. Helms (2864), R. H. H. Walker (2865), C. W. Allen (2619), J. J. Rice (2908), V. J. Odlum (3222), D. McK. McNab (2720), W. T. H. Scales (3240).—(Ex. Min. No. 58—Approved 14th April, 1942.)

The following temporary Squadron Leaders are granted the acting rank of Wing Commander whilst employed as Wing Commanders, with effect from the dates indicated: A. B. Anderson (1187), 5th January, 1942; R. I. Greenham (1188), 17th December, 1941; D. S. Thomson (1195), 18th December, 1941.

The following Flight Lieutenants are granted the acting rank of Squadron Leader whilst employed as Squadron Leaders, with effect from the dates indicated: J. G. Radford (1234), 9th January, 1942; E. W. Field (1247), D. B. Skewes (1281), W. T. Coyle (1680), 1st January, 1942; E. V. W. Pockley (3752), 22nd January, 1942.

Flight Lieutenant T. P. Mahon (1455) is transferred from the Reserve to the Active List with effect from 9th March, 1942.

Flight Lieutenant L. R. Flynn (3940) is promoted to Temporary Squadron Leader with effect from 22nd January, 1942.

The following are appointed to commissions on probation with the rank of Flight Lieutenant with effect from the dates indicated: Jack Barnes, M.B., Ch.B. (4590), John Maurice Barrett, M.B., B.S. (4593), Charles Ffranks Bernard, M.B., B.S. (4592), Lloyd Angus Commins, M.B., B.S. (4588), Malcolm Thomas Drummond, M.B., B.S., M.R.C.O.G. (4589), Alexander Wright McLaren, M.B., B.S., (4591), 9th March, 1942.

Reserve: Medical Branch.

The following are appointed to commissions on probation with the rank of Flight Lieutenant with effect from the dates indicated: James William Kenny, M.B., B.S. (3866), 2nd February, 1942; Arthur Paul Cahill, M.B., B.S. (4367), Thomas Dudley Hagger, M.B., B.S., M.D. (4364), Arthur Machen Hill, M.B., B.S., D.G.O., M.R.C.O.G., F.R.C.S. (4366), Herbert Stewart Moroney, M.B., B.S. (4365), Norman James Royle, M.B., B.S. (4369), 27th February, 1942.—(Ex. Min. No. 57—Approved 14th April, 1942.)

The following are appointed to commissions on probation with the rank of Flight Lieutenant with effect from the dates indicated: Guy Gavin Henn, M.R.C.S., L.R.C.P. (4573), 8th March, 1942; Arthur Linley Hare, M.B., B.S. (4419), 11th March, 1942.—(Ex. Min. No. 61—Approved 14th April, 1942.)

Correspondence.

MILITARY MEDICAL PROBLEMS.

SIR: I have attended a number of meetings of the British Medical Association when military medical problems were discussed. I venture with all respect to draw attention to one feature, namely, the different attitude adopted by those who had served in the army and those who had not.

The practical necessities of a total war effort influenced the former and they had the advantage of knowing what the average soldier had to do.

I will only add that statements made by some soldiers, especially recruits, can be described in the words of Dickens: "What the soldier says is not evidence." But the outstanding feature of the medical discussions is that comparatively few men have taken the trouble to find out what the problems were during the last war and consequently approach them in this war as if they were new.

In any piece of research the first step to be taken by anyone embarking on it is to find out what has already been done—in civil life a laborious business; in military matters not so difficult, because various military works have been published, official and otherwise.

The mobility in this war is the new feature, but the principles involved have not altered, though they want adaptation, and that evidently has been done.

I should be sorry not to acknowledge the fine work that has obviously been done in this war from which some practical suggestions will be made for use in civilian life whenever we return to it.

Yours, etc.,

JAMES W. BARRETT.

103-105, Collins Street,
Melbourne, C.1,
April 18, 1942.

PHYSICAL FITNESS AND EFFICIENCY.

SIR: Dr. Finckh's letter in your journal of March 28 invites a rejoinder. May I entertain this privilege? I am not a member of the medical fraternity, but I have been associated with this august profession for nearly forty-two years. Scores of medical men have visited my school, accepted my teaching, and entrusted me with complex cases involving the prescription and administration of bodily exercise. That should help to establish my prerogatives and extend to me also the courtesy of at least considering my criticism of the above letter.

Dr. Finckh's implications are obvious. He advocates fencing as a *sine qua non* for national physical fitness. But this is surely over-eulogizing the theme. Fencing has not any popular appeal because it savours too much of a middle age sport. It is too intricate to learn. Furthermore, it is too unnatural. It throws arms, body and legs into such awkward positions that skeletal and muscular deformities arise from its practice unless check exercises are instituted. Scolioses, *talipes plani*, and asymmetrical muscular hypertrophies have been noted in old fencers. In all natural activities muscular coordinations are involved which give organic satisfaction. Thus in walking and running the left arm and the right leg move together in well-established periodicities and *vice versa*. In right-handed throwing the left leg acts as a stabilizer and an arm-assistor, and so on. There are hundreds of such actions involved in bodily movements which are associated with instinct and survival. Fencing fails in this respect because it lacks this phylogenetic adaptation. It often takes years of application to conform oneself to fencing attitudes. That is why it is so unpopular, and men often throw it up in disgust or become bad fencers if they continue.

Dr. Finckh says modern fencing is a farce. I agree. That is because it still bears the taint of a drawing-room entertainment and the odium of the stage duel. Such romanticism has destroyed its real values, and even tangled fashionable and other women in its meshwork. This latter should have never happened, even if it be for obstetrical reasons alone. But *nous avons changé tout cela*. There are cultured men who cherish the fighting tradition and who scorn the frivolities of the decadent schools. To such robust souls the rapier can still invoke the ancient spirit of combat and become the instrument wherein everything is adapted save the fatal issue. In the ardour of such an assault the fullest psycho-physiological values bring the reward of such enlightenment. How can fencing be then any more than an esoteric art!

In viewing the larger aspect of national physical fitness we can see that fencing can only take a minor part. The kernel of any programme of national fitness must be the training of men and women in vigorous, well-disciplined activities, based upon biological principles. This ideal must be motivated by inspired leadership, which preaches the moral duty of personal fitness. Such leadership in physical education is of course foreign to the Australian. Our Lings, our Demenys, our Gulicks, our Jahns and Nissens have yet to be born.

I have pointed out elsewhere how the youths and adults of Germany and Russia view their training for physical fitness. There is seriousness, realism and planning for this aspiration *in excelsis*. Here one sees the "girding of the loins" for greater purposes than mere individual self-feeling. Contrast this with the superficial objectives of the British motive, the appeal to fitness through recreation and fun, and the approach to this conception through the liaison of sport champions and popular athletes who can at best only impart the veriest empirical knowledge. No wonder the scheme has been a failure, and we seem to be following in the same path.

Yours, etc.,

GEORGE Z. DUPAIN.

449A, Pitt Street,
Sydney,
April 14, 1942.

DOCTORS AND THE DRINK TRAFFIC.

SIR: There has been discussion lately about drunkenness in Australia. Military leaders have expressed anxiety at the loss of efficiency in soldiers. Most doctors are abstemious, many are total abstainers. What is the duty of the profession on this question? No body of men is so well placed to judge of the effects and results of alcohol drinking. Apart from use in pharmacy it has little therapeutic value. What doctor would order it regularly to his patients? The harm the traffic does is plain to see. Even politicians are reported as perturbed at the amount of drunkenness in Melbourne. They could in Sydney be similarly perturbed if they thought it discreet. Drunkenness is rife, the hotel bars are filled with our young men and women, wet canteens teach and persuade our young soldiers to drink. Many of us remember the hundreds of returned men in city streets after the last war, hopeless inebriates; and fathers and mothers wonder with anxiety if history is to be repeated as our own sons are returned to us. In the recent call up, ages thirty-five to sixty, I estimated 6% as hopeless alcoholics. One need not dwell on the social disease, broken homes, loss of efficiency, known to us all. Alcoholism is slowly but surely sapping our national vitality. In this call for preventive medicine doctors surely have a duty, a call for offensive, not defensive, action: both individually and as an association to oppose this influence so destructive of our young lives and nation.

Yours, etc.,

E. R. ROSEBY.

Boggabri,
New South Wales.
April 21, 1942.

CYCLOPROPANE.

SIR: I understand from recent letters of Dr. Gilbert Brown, of Adelaide, and Dr. Douglas G. Renton, of Melbourne, that the Medical Equipment Control Committee has classed cyclopropane amongst "drugs not considered essential, and which do not justify importation or manufacture".

Whilst realizing the numerous difficulties confronting this committee and the necessity at the present time for cutting down our imported drugs to a minimum, nevertheless I woud appeal, rather than protest, to them to make some further inquiries from those conversant with the advantages of this anæsthetic before coming to a final decision.

Perhaps their decision has been influenced by the fact that nitrous oxide is manufactured in this country and can fulfil the requirements of an anæsthetic with a wide margin of safety; it has a wide margin of safety in the individual requiring a minor procedure, in whom the asphyxial element matters little during a short superficial operation, but this is not the class of patient with whom we shall have to deal.

The inevitable anoxia necessarily associated with this anæsthetic gas exposes the shocked and/or anæmic patient to a grave risk of asphyxia. The cyanosis, which within limits is some guide to the degree of anæsthesia in the average patient, has no place as a guide in the anæmic individual, for he may, if his hæmoglobin is sufficiently low (about 9 grammes *per centum*), be asphyxiated without any noticeable colour change.

If the anæsthetist interprets this patient's tranquillity and unchanged colour for a sign of safe and satisfactory anæsthesia, then he may find himself rudely awakened to the fact that his patient is beyond recovery from asphyxia.

With this preliminary, we come to the position cyclopropane occupies in dealing with these shocked anæmic cases. Numerous occasions arise when the surgeon undertaking what at first sight appeared to be a minor procedure, finds on investigation that a major operation is necessary.

The anæsthetist, choosing nitrous oxide for its non-toxic effects in the "poor risk" patient, faces the problem of using a drug which anæsthetists do not consider a suitable one for major operative work. He has two alternatives: (*a*) push the nitrous oxide, enhancing its weak anæsthetic effect with a dangerous degree of anoxia, or (*b*) adding a more powerful anæsthetic when a liberal supply of oxygen may be given. The safer procedure is to add the more powerful anæsthetic; and what shall this be? Ether maybe, but not only will it take ten minutes or more to carry the patient into anæsthesia, but he will be submitted to what the anæsthetist to all intents and purposes wishes to avoid—an ether anæsthetic.

Without doubt, the safer, easier and best for these "poor risk" patients is to add cyclopropane rather than ether to the mixture, because the patient can be smoothly brought into anæsthesia in three minutes, and the oxygen in the mixture increased to a degree which will prevent any danger of asphyxia occurring.

We have no anæsthetic drug to take the place of cyclopropane when operations in the thoracic cavity are to be undertaken or when lung disease complicates operations of necessity. Although cyclopropane has some disadvantages (inflammability the chief one) they are far outweighed by the advantages.

Finally I would go so far as to say that if cyclopropane is put on the prohibited list of drugs, many lives, both of our soldiers and civilians, may be jeopardized.

Yours, etc.,

H. J. DALY.

143, Macquarie Street,
Sydney.
April 21, 1942.

ESSENTIAL HYPERTENSION.

SIR: I was interested to read in your issue of February 7, 1942, an article on the treatment of essential hypertension, by Dr. B. T. Shallard. He states: "The general medical treatment of hypertension today is much the same as it was twenty-five years ago", also that "the aim of therapy in hypertension is to relieve subjective symptoms and to prevent further elevation of blood pressure. The methods of treatment at our disposal may be regarded as symptomatic. They deal with the effects rather than the cause, which remains obscure." I fully agree with Dr. Shallard that such are the views of many medical men, but I totally disagree with him that such views are accepted by all. We as a fraternity have been apt to miss the obvious whilst searching in remote corners for the causation of disease.

To acquire hypertension it is necessary to suffer some pathological changes in certain tissues, either in the mechanisms which regulate pressure or in the peripheral vascular field. Every one of us is aware that bacterial poisons are most destructive agents to cell life, yet our practice in the past has been to condemn the imperfect metabolism of proteins, tobacco, alcohol *et cetera* as the primary factors in these conditions, and at the same time allow our patient's tissues to be bathed in a dilute solution of virulent bacterial toxins. For twenty-five years at least medical men have fought against the view that the presence of such organisms and their toxins are detrimental to health, and have shown it by their refusal to do anything to remedy the situation.

The body can deal more or less with such poisons for a number of years without the effect being obvious to the average medical mind, because by the time kidney or vascular changes are usually diagnosed the condition is already far advanced. We have long given up having our bodies ravaged by bugs, fleas and lice, yet we allow the most virulent organisms to breed within our tissues with impunity, pouring their deadly toxins into our blood streams, and then wonder why our tissues deteriorate. Such views I have held for many years and have applied them in my treatment of cases of raised blood pressure with remarkably satisfactory results, and I think all will agree that such views are rational. It is of course quite obvious that when the pathological changes have reached a certain stage any form of treatment is of no avail, but there are numbers of cases in their early and less advanced stages in which great benefit can be obtained. Recently a young woman came to me with a systolic pressure of 220. I told her that a woman of her age should not have such a condition. Examination revealed marked pyorrhœa. Within a week or so of having her teeth extracted her pressure had dropped to 160 systolic without any other form of treatment. One could quote a great many cases where the cleaning up of infections has been most efficacious in reducing pressure. This is usually supplemented by diathermy treatment through the kidneys as well as three grains of thyreoid extract daily. Personally I have never seen anything but good arise from the use of small doses of thyreoid extract. It not only dilates the peripheral vessels, but it helps to reduce the viscosity of the blood. I have long given up any other form of vasodilators as having no permanent value. Many think that by a casual glance at the gums and tonsils they have dealt with the infection question, and many an active streptococcal infection is missed for want of a culture.

The time has surely come when we both cease to breed these virulent organisms in our own bodies or allow our patients to do the same, any more than we would allow them to breed the *Spirochæta pallida* in their blood streams.

Yours, etc.,

SYDNEY PERN, M.R.C.S., L.R.C.P. (Eng.).

Ballarat,
Victoria,
Undated.

BISHOP HARMAN'S NIGHT VISION TEST.

SIR: The night vision test devised by Dr. N. Bishop Harman seems to me to be the best, and certainly the most simple yet devised.

I wrote to him for particulars and now quote his reply:

> You ask about the arrangements of the discs in the groups shown in the test. I tried many sorts of test form. Starting as was natural with those of different sizes, somewhat after the style of our day-light Snellen's tests. But I found that the grading of these was too coarse. So I turned to the experience we have with those who cannot see 6/60; we let them go closer and closer to the test and try if they can see 6/60, or 5/60 or 4/60 or 3/60 and so on. By having a fixed sized object for the test, and moving the subject nearer and nearer to it, or farther away, I got a far better grading. Also I found it easier to work. For the test object could be of reasonable size.
>
> The disc sizes are all the same—½". The half-inch discs are separated by a space of one-eighth of an inch. The discs number from four to seven, and they are so arranged as to look in their groups very much like each other. They are so arranged that when turned into different positions they all appear different, so that there are sixteen variations that can be shown.

After all, these night vision tests are simply tests of the threshold of vision, and like all clinical examinations are most useful when they are simple. It has seemed to me that tests for the precise time of dark adaptation are not necessary for practical purposes.

Dr. Harman's original paper appeared in the *British Medical Journal* of April 26, 1941.

Yours, etc.,

JAMES W. BARRETT.

103-105, Collins Street,
Melbourne,
April 22, 1942.

Australian Medical Board Proceedings.

QUEENSLAND.

THE following notice appeared in the *Queensland Government Gazette*, Number 13, of January 17, 1942.

The Medical Board of Queensland,
Brisbane, 8th January, 1942.

In pursuance of the Order of the Full Court of the Supreme Court of Queensland Appeal No. 12 of 1941 on Appeal from the Medical Assessment Tribunal between Max Michel, appellant, and the Medical Board of Queensland, respondent, and in particular Clause three (3) of the Declaration of the Court, it is hereby notified that the name of Max Michel, having been unlawfully erased from the Register of Medical Practitioners, the following extract from the Register of Medical Practitioners, Queensland, is published to be read as one with the list of medical practitioners, Queensland, for the year 1941 published in pursuance of the provisions of "*The Medical Acts*, 1939 *to* 1940," in the *Government Gazette* of the 26th May, 1941, No. 123, Vol. CLVI:

No. of Certificate.	Name.	Address.	Date of Registration.	Qualifications.
2227	Michel, Max	Equitable Life Building, 371 Queen Street, Brisbane	1937 8 July	L.R.C.P. and S., Edin.; L.R.F.P. and S., Glasg., 1936

By Order of the Board,
GEO. T. RIDDELL, Registrar.

THE undermentioned have been registered, pursuant to the provisions of *The Medical Acts*, 1939 *to* 1940, as duly qualified medical practitioners:

Archibald, Lorna Margaret, M.B., B.S., 1942 (Univ. Queensland), General Hospital, Brisbane.
Crosier, Joan, M.B., B.S., 1942 (Univ. Queensland), General Hospital, Brisbane.
Horn, Craig Angus, M.B., B.S., 1942 (Univ. Queensland), General Hospital, Brisbane.
Perkman, Salme, M.B., B.S., 1939 (Univ. Sydney), General Hospital, Ipswich.
Sinclair, Bruce Arran, M.B., Ch.M., 1925 (Univ. Sydney), c.o. Dr. A. D. D. Pye, General Hospital, Brisbane.
Squires, John Charles, M.B., B.S., 1942 (Univ. Queensland), General Hospital, Brisbane.
Ure, James Noel, M.B., B.S., 1942 (Univ. Queensland), General Hospital, Brisbane.

Obituary.

FRANCIS HENRY FURNIVAL.

WE regret to announce the death of Dr. Francis Henry Furnival, which occurred on April 22, 1942, at Turramurra, New South Wales.

JOHN THOMAS JONES.

WE regret to announce the death of Dr. John Thomas Jones, which occurred on April 23, 1942, at Mittagong, New South Wales.

WILLIAM MALCOLM SINCLAIR.

WE regret to announce the death of Dr. William Malcolm Sinclair, which occurred on April 25, 1942, at Ashfield, New South Wales.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Holman, Elton Dudley, M.B., B.S., 1941 (Univ. Sydney), Royal Prince Alfred Hospital, Missenden Road, Camperdown.

The undermentioned has been elected a member of the Tasmanian Branch of the British Medical Association:

Worcester, Alan, M.B., B.S., 1941 (Univ. Melbourne), Royal Hobart Hospital, Liverpool Street, Hobart.

Diary for the Month.

MAY 6.—Western Australian Branch, B.M.A.: Council.
MAY 7.—South Australian Branch, B.M.A.: Council.
MAY 8.—Queensland Branch, B.M.A.: Council.
MAY 12.—Tasmanian Branch, B.M.A.: Branch.
MAY 20.—Western Australian Branch, B.M.A.: Branch.
MAY 22.—Queensland Branch, B.M.A.: Council.
MAY 28.—South Australian Branch, B.M.A.: Branch.
MAY 28.—New South Wales Branch, B.M.A.: Branch.
MAY 29.—Tasmanian Branch, B.M.A.: Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility unless such a notification is received within one month.

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